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Abstract (Limit: 200 words)

This study examining the effectiveness of ambulatory cardiac monitoring (ACM). The study specifically examined three clinical uses of ACM: 1) the diagnosis of cardiac causes of syncope in the elderly; 2) the detection of life-threatening cardiac ischemia in asymptomatic patients after myocardial infarction; and 3) the selection of effective antiarrhythmic drug therapy in patients with malignant ventricular arrhythmias. In terms of syncope, the study finds that if procedures are sequenced in order of decreasing expected yield and increasing invasiveness, then ACM is indicated to establish the likely etiology of syncope. In terms of silent ischemia, the study finds that ACM is indicated, but that it is no better than other tests such as an exercise stress test or thallium scintigraphy. In terms of antiarrhythmic therapy, the study found the most cost-effective treatment was the use of electrophysiological studies followed by ACM.

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EFFECTIVENESS OF AMBULATORY CARDIAC MONITORING

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EFFECTIVENESS OF AMBULATORY CARDIAC MONITORING

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EFFECTIVENESS OF AMBULATORY CARDIAC MONITORING

EXECUTIVE SUMMARY

The term Ambulatory Cardiac Monitoring (ACM) refers to the use of various devices worn by ambulatory patients to monitor and record the electrocardiogram (ECG). The classic device for this purpose is known as the Holter monitor. Clinicians use ACM for a variety of clinical indications, to assist in diagnosing cardiac abnormalities that might be detected in an ECG recorded over a long period of time (typically 24 hours), during normal activity.

Our charge in this study was to evaluate the use of ACM for three clinical indications:

1. the diagnosis of cardiac causes of syncope in the elderly;
2. the detection of life-threatening cardiac ischemia in asymptomatic patients after myocardial infarction; and
3. the selection of effective antiarrhythmic drug therapy in patients with malignant ventricular arrhythmias.

This report is divided into three sections, each devoted to one of the clinical indications studied.

Section I, **The Use of Ambulatory Cardiac Monitoring in the Diagnosis and Management of Syncope in the Elderly**, summarizes the data currently available from the published literature on the effectiveness of ACM for this indication, in the context of a

sequential diagnostic strategy. If procedures are sequenced in order of decreasing expected yield and increasing invasiveness or risk, then ACM is indicated when a careful history and physical examination, followed by routine ECG, fail to establish a likely etiology for the syncope. This sequence will yield a diagnosis in slightly more than half of the elderly subjects presenting with syncope. Other diagnostic procedures that may be useful if ACM fails to reveal a probable etiology for the syncope are categorized by degree of invasiveness and speculation as to efficacy.

Section II, **Decision Analysis on the Use of Ambulatory Cardiac Monitoring for the Detection of Silent Ischemia in Asymptomatic Post Myocardial Infarction Patients**, presents a decision model that compares the estimated benefit of ACM, exercise tolerance testing (ETT), thallium-201 scintigraphy, and no testing in asymptomatic patients who have experienced an acute myocardial infarction. The outcome measure of effectiveness is estimated life expectancy. This analysis finds that any of the tests is better than no testing, and there is a very slight difference among the three testing choices. Non-invasive testing after myocardial infarction in asymptomatic patients provides approximately 4 months gain in life expectancy for a 55 year old man (with life expectancy of 16 years). The relative gain in life expectancy with noninvasive testing increases with age. Adequate data on post-infarction patients with silent ischemia are lacking, so this decision analysis included estimates based on data for symptomatic and non-

post-infarction patients.

In Section III, **Effectiveness of Ambulatory Cardiac Monitoring: Evaluation of Antiarrhythmic Agents**, we use decision analysis to compare three alternatives for evaluating the effectiveness of antiarrhythmic agents: ACM alone, ACM followed by exercise tolerance testing (ETT), and electrophysiologic studies (EPS). The outcomes considered in this analysis include the proportion of patients for whom an agent can be selected, the rates of drug-associated aggravation of the arrhythmia, rate of recurrence of the arrhythmia, and the number of hospital days and of trials needed for drug selection. With a series of decision models, we illustrate that patients receiving ACM or EPS have essentially the same probability of having an effective agent identified, and both methods are superior to ACM followed by ETT for selecting an antiarrhythmic agent. It is likely that the different methods identify agents for different sets of patients. A cost-effectiveness comparison using the other measures of effectiveness and resource utilization suggests that the strategy of EPS followed by ACM is likely to provide a greater expected utility than the strategy of ACM followed by EPS, but at additional health resource cost. We caution that the available data for these analyses were extremely limited, and that conclusions can not be drawn with great confidence.

The major limitations of these three evaluations come from the

paucity of data for some important steps in the analyses. The strength of these evaluations lies in identifying the available data as well as the data still needed. Sensitivity analyses illustrate how influential various pieces of data are on the outcomes. We also discuss current ongoing clinical studies that may soon provide some of the data now unavailable.

OVERVIEW

Purpose and Objectives

This project extends the meta-analytic study of the effectiveness of ambulatory cardiac monitors (ACMs), completed by the Technology Assessment Group of the Harvard School of Public Health, and submitted to HCFA as the report, "A Review of the Evidence for the Effectiveness of Ambulatory Monitoring and Recommendations for Reimbursement Policy," dated April 30, 1990 (HCFA contract order number 89-1519).

The purpose of the current project is to carry out additional analyses to explore the effectiveness of ACMs for specific diagnostic uses. We developed models for decision analysis to guide appropriate use of ACM for each of the clinical indications under study. We focused on three clinical indications for ACM:

1. the diagnosis of cardiac causes of syncope in the elderly;
2. the detection of life-threatening cardiac ischemia in asymptomatic patients after myocardial infarction; and
3. the selection of effective drug therapy in patients with malignant ventricular arrhythmias.

The objectives of this study are: 1) to provide HCFA with information, derived from the published literature, on effectiveness of ACMs for specific indications; 2) to develop models for decision analysis for determining the appropriate use of ACMs, based on our findings about effectiveness of ACMs for the specified clinical indications.

Although ACM has been a part of routine clinical practice for three decades, it remains a prime example of a technology that is widely used and has not been thoroughly assessed for effectiveness. Approximately 1.2 million ACM episodes were reimbursed by the Medicare program in 1989 (telephone communication, M. Borowitz, HCFA). Guidelines for appropriate use of ACM have been published by professional societies such as the American College of Physicians, the American College of Cardiology and the American Heart Association.[1,2] For lack of formal technology assessments, these guidelines are formulated through a consensus process, reflecting accepted practice and expert opinion about effectiveness.

In practice, ACM is used for a wide variety of purposes, including diagnosis, prognosis, and therapeutic monitoring. It is also used in patients with diverse clinical indications, from palpitations to myocardial infarction. If different patient characteristics are also considered, this creates a large number of possible conditions for which ACM effectiveness should be assessed. In addition, thorough technology assessments would compare ACM with other competing noninvasive tests, such as exercise tolerance

testing and dipyridamole thallium scanning. This quickly adds up to a complex matrix of potential technology assessments for ACM, of which few actually exist in the published literature.

The paucity of rigorous comparative studies evaluating the effectiveness of ACM is especially vexing for the Health Care Financing Administration, as scientific evidence of effectiveness is not available to provide a sound basis for Medicare coverage policy of ACM. Our intent with this project is to show how evidence from the literature may be synthesized through the framework of decision analysis to provide some guidance in appropriate usage of ACM. We also will identify areas where data are especially weak or scanty.

Background

Our first study for HCFA (April, 1990) assessed the effectiveness of ACMs for: 1) diagnosing cardiac causes of syncope, dizziness, and palpitations; 2) assessing the efficacy of antiarrhythmic therapy in patients with atrial fibrillation, premature ventricular complexes, Wolff-Parkinson-White syndrome, and possible proarrhythmic effects of antiarrhythmic therapy; and 3) detecting asymptomatic ischemia in patients with coronary artery disease and post myocardial infarction.

We collected and reviewed nearly 800 articles reporting studies of these clinical indications that included ACMs. From our review of the published literature, we concluded that ACM has not been comprehensively assessed in the 30 years since the first

ambulatory monitor was introduced by Holter.[3] Quantitative synthesis (meta-analysis) of the published literature provides a way to attempt to answer questions about effectiveness of ACMs, using data from studies that were not necessarily designed to address such questions.

In brief, our 1990 study yielded the following conclusions. For diagnosis of cardiac causes of infrequently occurring dizziness and palpitations, transtelephonic transmission of the electrocardiogram produced by an ACM may be more effective than a standard ACM. In patients with syncope, the diagnostic effectiveness of ACM varies widely, depending upon the frequency of syncopal episodes in individuals and the rate of arrhythmias occurring in the normal population (a rate that increases with age).

For therapeutic monitoring of the effectiveness and safety of antiarrhythmic drugs, the ACM is effectively used in clinical trials. In patients with potentially malignant arrhythmias, the role of antiarrhythmic agents is uncertain. Antiarrhythmic agents may not prolong life and may increase risk of sudden death, especially in post-infarction patients. Thus, the effectiveness and appropriateness of ACM for therapeutic monitoring of antiarrhythmic therapy for potentially malignant arrhythmias remains unclear.

In patients with previous atrial fibrillation, detection of a recurrence following cardioversion can be carried out effectively with ACM, but a standard 12-lead ECG is likely to be as effective.

If paroxysmal atrial fibrillation occurs with symptoms, then patient-activated transtelephonic transmission of the ECG is also likely to be effective for detection.

In patients with asymptomatic (silent) ischemia, few studies have compared the diagnostic and prognostic yield of ACM and exercise tolerance testing. **The one clear indication for use of ACM instead of exercise testing was for patients who cannot tolerate exercise.**

After completing the preliminary study of ACM in 1990, we accepted HCFA's request to pursue certain indications in more detail. Based on discussions with Michael Borowitz and Stephen Jencks of HCFA, we chose to focus on three indications, and to add decision analysis to our methods.

Overview of Research methods

In this study, we assessed the effectiveness of ambulatory cardiac monitoring for three indications:

1. diagnosis and management of syncope in the elderly;
2. detection of asymptomatic (silent) ischemia, after myocardial infarction;
3. therapeutic monitoring of antiarrhythmic agents for malignant arrhythmias.

For each of the three clinical indications, we performed comprehensive searches of the published literature to update our

collection of articles. We used computerized searching of MEDLINE, reviewed reference lists from relevant articles, and also reviewed Current Contents for the most recent publications.

Review of literature, and development of decision models

Each of our experts in clinical decision analysis (Drs. Antczak-Bouckoms, Frazier, and Lau) has taken primary responsibility for one of the three clinical indications. Within this report, the studies for each indication are discussed separately, including detailed information on data sources and modeling.

For the syncope study, we summarize and review findings from the literature and discuss a schema for sequencing diagnostic procedures. The incremental diagnostic value of ACM is discussed with regard to preceding medical history, physical examination and routine ECG. Potential diagnostic procedures that may follow unsuccessful diagnosis by ACM are discussed.

For the antiarrhythmic and silent ischemia studies, we developed clinical decision models, based upon clinically relevant research questions. We derived estimates for the models from the literature when available. We used a range of estimates to perform sensitivity analyses. Limitations of available data are discussed for each indication.

For the three clinical indications we focused on the following research questions:

1. Syncope

Research Question: What is the optimal role of ACM, with respect to other potential diagnostic procedures, in the diagnosis and management of syncope in the elderly?

2. Silent Ischemia

Research Questions: In patients post acute myocardial infarction, how does ACM compare with exercise tolerance testing and thallium scanning in diagnostic accuracy? What is the probability that ACM, exercise tolerance testing, or thallium scanning will detect cardiac ischemia, leading to effective treatment? How do patient outcomes in terms of life expectancy compare for the three testing modalities?

3. Therapeutic monitoring of antiarrhythmic agents

Research questions: What is the probability that ACM will identify an effective and safe antiarrhythmic agent? How does this capability compare to electrophysiologic (EP) testing?

Types of Ambulatory Cardiac Monitors

The term ambulatory cardiac monitor (ACM) refers to a variety of devices that may be worn by ambulatory patients to monitor and record the electrocardiogram (ECG). The classic device for ambulatory monitoring, the Holter monitor, was first introduced in 1961.[3] The Holter monitor permanently records and provides full disclosure of the ECG for extended periods, usually 24 hours. Review (often computer-assisted), interpretation, and reporting usually require at least one day beyond the period of recording. Charges vary for the basic 24 hour unit of monitoring, but usually are multiples of the charges for short period event recorders, described below. The Holter monitor remains the standard against which other newer devices are measured.

Newer ACM designs have the capability to continuously monitor the ECG for long periods, and to record the ECG only when prompted to do so. With real time cardiac monitors, each complex is evaluated as it occurs (in "real time") according to an algorithm programmed into the machine. Only those complexes interpreted as abnormal by the program are recorded. Interpretation and reporting can be done very rapidly. Newer units can also provide full disclosure recording capability. Existing programs perform as well as Holter monitors for identification of ventricular arrhythmias, but less well for atrial fibrillation, pacemaker rhythms, A-V block and junctional rhythms.[4] Charges approximate those for Holter monitoring.

The tape loop monitor, a short-term event recorder,

continuously records a few minutes of the ECG. When the wearer presses a signal button, the machine permanently stores the preceding one to four minutes of ECG and approximately one minute of post-signal ECG. The record can be transmitted by telephone to a central facility for immediate or delayed interpretation. Existing models do not have full disclosure capability, although it seems feasible to develop it, and require patient cooperation in order to make a permanent record of the ECG that was monitored simultaneously with the symptoms. Charges are substantially lower than those for the Holter or real time monitor, making it practical to monitor patients for long periods when the symptomatic events are very infrequent.[5,6]

Because each session of ACM recording produces voluminous data, technicians generally rely on computerized analysis systems to assist them in reviewing the ACM results. These systems screen recordings for deviations in the ECG, and can replay recordings at high speeds for faster review. Of course, accuracy of these systems, including accuracy of the technician who uses the system, partly determines the accuracy of the ACM result.

For purposes of our study, we assume that full disclosure of the ECG, as provided by the standard Holter monitor, is the most reliable method of ACM. With real-time monitors that do not provide full disclosure, the clinician has no way to judge whether any abnormal episodes have been missed. Unless stated otherwise, we assume the use of an ACM for the standard 24-hour monitoring

period, with continuous recording and full disclosure of the EKG for the entire monitoring period. We further assume that computer-assisted analysis of the ACM recording is highly accurate, and that the various analysis systems on the market are comparable in their accuracy.

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THE USE OF AMBULATORY CARDIAC MONITORING IN THE DIAGNOSIS AND MANAGEMENT OF SYNCOPE IN THE ELDERLY

Introduction

This study examines the appropriate use of ambulatory cardiac monitoring (ACM) in the diagnosis and management of syncope in the elderly. By syncope we mean a sudden, transient loss of consciousness, with loss of postural tone, and with spontaneous recovery. ACM refers to any one of several devices, all of which are designed to sense and record the electrical signals of the scalar electrocardiogram (ECG). We begin with a brief description of the clinical attributes of syncope, continue with a discussion of strategies for determining the cause of syncope, and conclude with aspects of the problem of syncope that remain to be resolved.

Clinical Features of Syncope

Syncope is a common problem among adults. In a prospective study of men and women averaging 87 years of age and living in an institutional setting, the annual incidence of syncope was 6%, and given an episode, the recurrence rate was 30%.[1]

The harms associated with syncope are of three kinds: (1) those hazards related to the conditions causing the syncopal episode; (2) those hazards related to the trauma of the fall; (3) and those risks borne by others from a syncopal episode of, for

example, the driver of an automobile. Some estimates of the magnitude of these hazards are available.

As noted above, the first group of hazards are those related to the underlying condition that caused the episode of syncope. If we pool the experience of elderly patients with all likely causes of syncope, the risk of death for the individual patient who has had at least one syncopal episode approximates 27% over the ensuing two years.[2] The usefulness of this prognosis is enhanced if, instead of lumping all causes of syncope together, we disaggregate them into cardiovascular causes, non-cardiovascular causes, and syncopal episodes to which we cannot assign a cause. The experience of a group of patients averaging 71 years of age, the etiology of whose syncope was described in this way, has been reported.[2] For those with a cardiovascular cause of their syncope, the chance of dying over the ensuing two years was 38.1%. Those with non-cardiovascular etiologies for their syncope had a 21.6% risk of dying over the subsequent two years, while those for whom no specific cause of their syncope could be established had a risk of death over the next two years of 20.4%. For comparison, the mortality from all causes expected in a cohort drawn from the general population passing through the two year period of 70 to 72 years of age is 4.1% of the original, or live birth, members of the cohort or 5.9% of those members of the cohort who reached age 70.[3]

There is less information about the second group of hazards, those related to the trauma of the fall brought on by the syncopal episode. The available data suggest that the rate of injury per

episode of syncope in the elderly may be as high as 35%. Of these, up to a sixth of the injuries are substantial: fracture, subdural hematoma, or the consequences to the index case of automobile accidents.[4,5]

The third group of hazards, those related to risks borne by others in the vicinity of the index case -- who might be, for instance, the driver of a car -- has received insufficient attention.

The usefulness of this typology of hazards is determined primarily, but not exclusively, by its potential identification of modifiable risks. For example, interest in the cardiovascular causes of syncope is reinforced by the recognition that the category as a whole carries increased risk of death, and that some diagnostic categories within this group, if identified, are treatable, with a net reduction in risk. These categories include bradyarrhythmias such as complete heart block, and their treatment with implanted pacemakers.[6] In the class of non-cardiovascular causes of syncope, major treatable diagnostic categories include exposure to medicinal drugs that produce orthostatic hypotension as an adverse side effect.[7]

Interest in diagnostic strategies for syncope in the elderly, then, is driven by the hazards associated with syncope, the knowledge that some causes of syncope are treatable with net benefit to the patient (although we have not found controlled studies on this important point), and that, in general, securing the benefits of treatment depends on knowing the cause of syncope.

Another reason for interest in diagnostic strategies has to do with the value the patient places in knowing the cause of his or her syncope, whether or not the cause is treatable.

ACM, the immediate objective of this study, is one of a group of diagnostic interventions appropriate to the workup of syncope. We will suggest guidelines for its use, but also attempt to put it in the context of other modalities that may be employed in the diagnosis of syncope.

A large number of discrete causes of syncope are identified in the medical literature.[5,7,8] Most such studies are retrospective series collected at a single location and are susceptible to the usual problems of ascertainment bias. Despite this source of uncertainty, three broad conclusions emerge from the published information. First, a large fraction, ranging from one third to two thirds in various series, of those with new onset of syncope remain undiagnosed after a detailed, expensive and, often, an invasive workup.

Second, the frequency distribution of diagnosable causes of syncope varies with the age of the patient. Both points are addressed in Table I-1, taken from a paper by Kapoor and colleagues.[2] In both young (mean age 39) and elderly (mean age 71), just under half had no cause established for their syncope. Further, Table I-1 demonstrates that in those whose syncope could be assigned a potential cause, there was a difference in the frequency of cardiovascular and non-cardiovascular etiologies between the two age groups. It follows that the design of a cost-

effective diagnostic strategy will at least take account of age. To the extent that appropriate data are available, the present study will focus on the group of those subjects who are 65 and older.

Third, the elderly patient's syncope is likely to be multifactorial, and frequently will include a component derived from medications being taken for problems other than syncope.[7,8,9]

Diagnostic Strategies Including Use of ACM

Principles

The objectives of a specific diagnostic pathway are to achieve a credible diagnosis with the minimum number of tests, whose aggregate risk is no greater than the expected benefit that will flow from knowledge of the diagnosis. The word "credible" emphasizes that the results of all diagnostic tests in the real world are probabilistic, hence all diagnoses are too. The tolerable uncertainty surrounding a particular diagnosis in a particular patient is a complex function of identifiable risks and benefits, and the patient's preferences about those risks and benefits. In this analysis, we shall set a relaxed standard of proof of diagnosis: the first identification of an etiology that could explain a syncopal episode. Exclusion of all other etiologic possibilities will not be required.

Application of these principles yields two simple rules for the design of a diagnostic pathway: diagnostic tests will be

undertaken in the order of descending yield in the population of concern, and in the order of ascending risk to the patient. Simultaneous application of the two rules may lead to a conflict at certain points in the diagnostic pathway, partly because of insufficient information about the characteristics of the tests, but as a practical matter, the two rules work well through the point of application of ACM in the diagnostic pathway.

Operational Guidelines

Specific diagnostic interventions are arranged in a sequence according to the principles noted in the preceding section and relevant attributes of the patient, such as age and the age-related spectrum of etiologies of syncope.[2,7,10] Each new patient belonging to that group is started along the same diagnostic pathway. Further diagnostic interventions are stopped as soon as a credible diagnosis is established according to the criteria discussed in the previous section (entitled Principles).

The Sequence of Diagnostic Interventions Up To and Including Use of ACM

History and Directed Physical Examination

There is broad consensus on the design of the first components of the diagnostic pathway.[5,9,11,12,13,14] It begins with a careful history and physical examination, including a neurological evaluation and, usually, assessment of the effects of carotid massage. These first steps in the diagnostic evaluation are listed

in Table I-2. In the elderly, the combined diagnostic yields of the history and physical examination approximate 25% of subjects with new onset of syncope.[2] Examples of potentially treatable etiologies of syncope that could be detected by these diagnostic steps are also shown in Table I-2.

Standard 12-lead ECG

The next step in the diagnostic pathway is the performance of a standard 12-lead ECG, which adds a diagnostic yield of approximately 9% to the 25% derived from the history and physical examination, as shown in Table I-2.[2]

Ambulatory cardiac monitoring

If no credible diagnosis has been made as a result of steps one and two, the next intervention is ambulatory cardiac monitoring (ACM), usually carried on for 24 hours, or for multiples of a day. There are several types of equipment available for ACM, each with differing strengths and limitations, as noted in the Introduction. We describe here the diagnostic yield of this technology, and note situations where use of a particular type of equipment seems advantageous.

Potential results of ACM

The results of ACM can be used for a variety of clinical purposes. In the present context, the objective is to establish a relation between syncope and a cardiac dysrhythmia. Given a technically adequate period of ACM, four general results are possible. They are summarized in the following paragraphs. The

frequency of their occurrence in a population with syncope but unselected for age is shown in Table I-3; the data are from Kapoor 1991.[12]

(1) Both symptoms and dysrhythmias thought to be potential causes of syncope are absent during the period of observation; this result is indeterminate.

(2) Symptoms are absent, but the record includes dysrhythmias that have been associated with syncope in others. This is the most common result of ACM for the diagnosis of syncope in the elderly. It is particularly difficult to interpret because of the increased prevalence of asymptomatic dysrhythmias with advancing age and the possibility that other etiologies not now present (such as drugs promoting postural hypotension) may have contributed to the original episode.[15,16,17] We return to this matter below.

(3) ACM demonstrates that a syncopal episode occurred without a concurrent dysrhythmia. This is a conclusive result which, for practical purposes, rules out a dysrhythmia as a cause of syncope, and directs attention toward other causes.

(4) ACM shows an episode of abnormal rate or rhythm at the time of an episode of syncope or presyncope. This too is a definitive result; it focuses treatment planning on the future prevention or suppression of the dysrhythmia.

Note that the population described in Table I-3 is not restricted to the elderly. As a result, it tends to underrepresent

the frequency of cardiovascular causes of syncope, although the published data do not permit a quantitative estimate of the size of the effect. The results, however, do support the conclusion that diagnostically useful information is obtained from ACM in more than 21% of the subjects monitored for syncope that remains unexplained after the basic workup. This figure represents the outcomes in two groups: the 4% with simultaneous dysrhythmia and syncope, and the 17% with syncope and no simultaneous dysrhythmia.

Observations of dysrhythmias during ACM

There are many reports of the identity and frequency of occurrence of the dysrhythmias detected during ACM. The patients described in Table I-4 are drawn from the three series in which all of the subjects were 60 or older, and almost all were over 65, the age group of greatest interest to the Health Care Financing Administration (HCFA).[2,7,18] The dysrhythmias assigned as causes for the subjects' syncope in these three series are indicated.

Table I-4 reveals wide variation in the frequency of specific causal cardiac mechanisms of syncope across the three groups. The numbers of subjects are small, and some variation is to be expected on those grounds, but other sources of variation are likely as well. For example, the defining characteristics of some cardiac mechanisms such as sick sinus syndrome (SSS) vary across authors. In addition, some authors, in the face of complex dysrhythmias and other co-existing causes of orthostatic hypotension, made a judgment as to which one was responsible for the episode of

syncope. Finally, given the differences in the age distributions across the three groups of the elderly, it is possible that there were real differences in susceptibility to specific dysrhythmias.

It is apparent that ACM can detect dysrhythmias if they are present. In a small percentage of patients with syncope, ACM can establish a causal link between an episode of a dysrhythmia and an episode of syncope. The important question remains: Does the discovery of the dysrhythmia and its type have valued consequences for the patient? First, regarding technical outcomes, the demonstration of net, statistical benefit may depend on the outcome variable that is chosen in a particular instance. For example, administration of Class 1 antiarrhythmic agents may suppress dysrhythmias in a patient, but simultaneously may increase the risk of death.[19,20] In contrast, ACM can detect intermittent bradyarrhythmias as a cause of syncope. Treatment with an implanted pacemaker is beneficial both for the prevention of syncope and for improvement in survival.[6]

A second kind of outcome is the ability to make a diagnosis, or a judgement about prognosis, independent of the availability of treatments to alter it. Examples of general prognostic conclusions based on ACM in the elderly were cited in an earlier section of this study, but agreement on prognostic details is lacking.[1,4,21,22,23] In any event, the value attached to information of this sort is highly individual, which makes it very difficult to include these

kinds of subjective benefits of ACM in a cost-effectiveness analysis of the modality.

Duration of ACM

If a trial of ACM yields an indeterminate result with respect to the cause of syncope, the question is whether to continue ACM or to move down the investigative sequence to the next diagnostic intervention. Bass, et al. report on a consecutive series of 95 patients, median age of 66, the etiology of whose syncope was not discovered after history, physical examination and routine ECG.[24] ACM in this group yielded the first manifestation of major ECG abnormalities on day 1 in 15%, on day 2 in 11%, and on day 3 in 4%. The complement to these findings is the observation that among the patients who had episodes of dizziness or syncope without a concurrent arrhythmia (that is, non-cardiac syncope or pre-syncope), 14% were found on day 1, 2% on day 2, and 4% on day 3 of ACM. Considering the yield of useful information in this group of patients by duration of monitoring, 28% benefited diagnostically by one day of ACM, an additional 12% by two days, and an additional 7% by three.

Summary of the indications for the use of ACM in the diagnosis of syncope in the elderly

The diagnostic strategy for establishing the cause of syncope in the elderly depends upon two principles: the use of diagnostic interventions in order of decreasing expected yield, and in order of increasing invasiveness or risk. Within this context, ACM is

indicated when a careful history and physical examination, and routine ECG, fail to establish a likely etiology for the syncope.

Given those indications, is there some simple test that could be applied at the point of service to verify the appropriateness of proceeding to ACM? Documenting the performance of a careful history and physical examination before monitoring for syncope does not seem to be an operationally feasible way of establishing a set of preconditions for ACM at the point of service. The reason is that the number of potential etiologies of syncope is large, and even though, for example, many are discoverable in principle from the history, there is no practical way to verify whether a failure to diagnose was due to failure to elicit the history on the physician's part, inability to cooperate on the part of the patient, or the presence of an etiology that could not be established from the history.

It does seem clear, however, that it would be possible to require the performance of ACM before going on to some of the more invasive and expensive tests described in the next section, tests whose performance in establishing etiologies of syncope in the elderly are not as well studied as those of the Holter monitor.

Diagnostic Strategies After Use of ACM

The preceding sections have addressed the main question of this part of our report: When should ACM be used for diagnosis of the underlying cause of syncope? Thoughtful application of the diagnostic maneuvers previously discussed -- history, physical and neurological examination, routine ECG and a period of ACM -- will yield a diagnosis in slightly more than half of the elderly population presenting for study. A number of additional diagnostic interventions have been applied to the residual, undiagnosed cases. Unfortunately, none have been compared for diagnostic efficacy in randomized trials, or studied for their content of information in addition to that supplied by medical history, physical examination and routine ECG, with and without ACM. The need for study of the tests is made more urgent because some are both noninvasive and promising.

The categories under which they are listed below are based on invasiveness, on the one hand, and speculation (in the absence of full evaluation) as to efficacy, on the other.

(1) **Non-invasive, efficacy deserves full study**

a. Tilt table, with and without isoproterenol

b. Signal-averaged ECG

c. Real time and tape loop monitors for infrequent events

(2) **Non-invasive, but low yield as noted**

a. Exercise tolerance test

b. CT, electroencephalogram; low yield unless focal neurological signs

(3) **Invasive**

a. Electrophysiologic studies; unknown efficacy for brady-dysrhythmias

b. Cerebroangiography; low yield unless focal neurological signs

c. Cardiac catheterization

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Table I-1

AGE OF PATIENTS AND CAUSES OF SYNCOPE*

Etiology of Syncope	Age Group	
	Mean age (range)	39 years (14-59)	71 years (60-90)
	Sample size [n]	[190]	[210]
		Percent of Age Group [n]**	Percent of Age Group [n]**
Cardiovascular		16.8 [32]	33.8 [71]
Non-cardiovascular		37.9 [72]	26.7 [56]
Unknown		45.3 [86]	39.5 [83]

* From [2]

** Probability that the difference in distribution of etiologies between the two age groups could have arisen by chance alone is less than 0.01 (chi square = 15.82; 2 d. f.)

Table I-2

BASIC EVALUATION OF TRANSIENT LOSS OF CONSCIOUSNESS IN THE ELDERLY*

Diagnostic maneuver	Examples of etiologies potentially discoverable via the diagnostic maneuver	Cumulative yield of diagnoses as % of new cases of syncope
A. Medical history	Orthostatic hypotension from medication Myocardial infarction (MI) Situational syncope (post-prandial, micturition, defecation, post-tussive) Vasovagal/vasodepressor	
B. Physical examination	Valvular heart disease Orthostatic hypotension of all causes Cerebrovascular events Brady-dysrhythmias Tachy-dysrhythmias Carotid hypersensitivity	25% (A+B)
C. Routine ECG	Acute MI Brady-dysrhythmias Tachy-dysrhythmias	34% (A+B+C)

* From [2], which specifically describes subjects most or all of whom would be eligible for Medicare coverage.

Table I-3

UNEXPLAINED SYNCOPE OR PRE-SYNCOPE: OBSERVATIONS FROM AN EPISODE OF AMBULATORY CARDIAC MONITORING (ACM) IN SUBJECTS UNSELECTED FOR AGE*

Observation	Frequency
Dysrhythmia with simultaneous syncope	4%
Dysrhythmia without simultaneous syncope	13%
Syncope without simultaneous dysrhythmia	17%
Neither syncope nor simultaneous dysrhythmia	69%
Total	103%**

* From [12]

**Said to exceed 100% "because of missing information from two studies" of eight quoted in the review.

Table I-4

IDENTIFICATION BY ACM OF DYSRHYTHMIAS ASSIGNED AS CAUSES OF SYNCOPE AND PRE-SYNCOPE IN THE ELDERLY

Causal cardiac mechanism*	Age, in years, of study population with unexplained syncope, [reference], and frequency of dysrhythmia in subjects		
	60-90 [2]	87±6 [7]	60+ [18]
VT	16%	0%	9%
SVT	-	1	-
SSS/Sinus arrest	6	1	3
Bradycardia	1	-	-
Heart block, all types	3	1	1
Brady-tachy syndrome	-	3	-
Total diagnostic yield in %	26	6	13

* VT = ventricular tachycardia; SVT = supraventricular tachycardia; SSS = sick sinus syndrome.

DECISION ANALYSIS ON THE USE OF AMBULATORY CARDIAC MONITORING FOR THE DETECTION OF SILENT ISCHEMIA IN ASYMPTOMATIC POST MYOCARDIAL INFARCTION PATIENTS

Introduction

Patients who have experienced acute myocardial infarction (MI) have significant coronary artery disease. Early diagnosis and prompt treatment of acute MI with modern therapies such as thrombolytic agents, beta-blockers, nitrates, magnesium sulfate, anticoagulants, and anti-platelet agents may result in salvaged myocardium and a significant reduction in the risk of early death. Many survivors, however, have residual coronary artery disease (coronary artery stenosis not in the immediate infarct zone; non-Q wave myocardial infarction) that places them at risk of future ischemic events and subsequent death. Among recent studies, the one-year mortality rate after acute MI is reported to be approximately 10%. Seventy-five percent of the first year mortality occurs in the first 100 days post infarct, decreasing and remaining relatively constant at a rate of 3 to 6% a year, after the first year.[1]

A number of risk factors have been identified that are associated with early deaths. Patients with continuing chest pain after acute MI are typically selected for coronary angiography and considered for treatment with angioplasty or coronary bypass grafts. A positive exercise electrocardiography (ETT) soon after MI has been found to carry a poor prognosis; 27% one year mortality

was found in patients with exercise induced ischemia, compared to 2% mortality in patients without ischemia on exercise.[2]

Most authorities now recommend predischarge submaximal ETT.[3] If the result is positive, coronary angiography will be recommended. If the test is equivocal, or if the patients cannot exercise to a satisfactory degree, ambulatory cardiac monitoring (ACM) or persantine thallium-201 scintigraphy are recommended. Submaximal ETT, ACM, and thallium are all non-invasive tests. None is perfectly accurate, and each has limitations.[4]

Silent ischemia among patients with coronary artery disease is an area under active investigation.[5,6,7,8] It has an estimated incidence of 34% among patients with positive ETT,[1] 44-84% among symptomatic patients, and 20-30% in patients who had sustained MI.[9] In an often quoted early study, the prognosis of post-MI patients with silent ischemia was found to be similar to that for patients with symptomatic ischemia.[2] However, recent data are lacking. Due to an apparent lack of efficacy of surgical treatment in the subgroup that included post-infarction patients with silent ischemia in the CASS study, the need for studying asymptomatic post-MI patients has been the subject of controversy.[10,11]

The Decision Problem

The role of ACM for the detection of silent ischemia in asymptomatic patients following acute MI has not clearly been established. Three areas where ACM may be applied in the evaluation of silent ischemia in asymptomatic post MI patients are:

1. ACM could be used in place of the current standard practice of submaximal ETT or thallium-201 scintigraphy.
2. ACM could be used as an additional test after a negative ETT in an attempt to improve the detection of silent ischemia.
3. ACM could be used as an additional test after an intermediate positive ETT to further delineate the severity of the ischemic heart disease.

Although it may be possible for ACM to identify additional patients with residual coronary artery disease by detecting silent ischemic episodes among patients who had a negative submaximal ETT, current literature does not support this hypothesis. Some authors suggest that since both ACM and ETT are based on similar physiologic principles, there is little to be gained from performing ACM in addition to ETT.[1,12,13] Patients undergoing ETT are stressed so that ischemia is more likely to occur, whereas patients with ACM perform normal daily activities and may not achieve as high a cardiac demand. In addition, the prevalence of residual CAD is significantly lower among patients having a negative ETT. Data supporting this view are not available from the literature; estimation is based on the prevalence of silent ischemia among asymptomatic patients reduced by those detected by a submaximal ETT. Indeed, one study identified no additional cases when ACM was performed after the initial ETT.[14]

The use of ACM after ETT to further delineate the severity of

ischemic heart disease cannot be considered to be a use of ACM in asymptomatic patients. This use of ACM is in patients identified by ETT to have some degree of residual CAD.

Our purpose in this analysis was to compare the relative efficacy of routine predischarge submaximal ETT, ACM, and thallium-201 scintigraphy for the detection of silent ischemia among asymptomatic survivors of acute MI. The comparison of ACM to either submaximal ETT or thallium-201 scintigraphy is primarily one of comparing the sensitivities and specificities of the tests, and the trade-offs between sensitivity and specificity.

The Decision Analysis

This decision analysis primarily focuses on estimating the relative efficacy of various non-invasive tests in detecting silent ischemia among post-infarction patients, specifically, on the comparison of sensitivity and specificity of the tests. Data on the prognosis and outcomes among these patients are unavailable or not well established. Data from non-silent ischemic patients will be used as proxy where data for silent ischemic patients are unavailable. This is done to provide estimates of life expectancy of various outcomes needed for the decision analysis. This approach may not give a reliable estimation of the magnitude of life expectancy of these outcomes. However, the effect of this approach on the relative differences of life expectancy among the strategies is likely to be be small, and allows us to make relative comparisons among the diagnostic strategies. The following assumptions were made to allow the decision analysis to be performed.

Assumptions

1. Patients are able to perform submaximal exercise and do not have left bundle branch block that precludes the interpretation of ETT or ACM.
2. Silent ischemic episodes detected by ACM identify patients at risk of future cardiac events, and therapeutic intervention will reduce early deaths. In one study,[15] two-thirds of the patients with post-infarction

silent ischemia developed angina during the follow-up period of 21 months. Although there is no conclusive evidence that the prognosis of patients with silent ischemia is altered by drug therapy,[9] we will model surgical interventions with angioplasty or CABG as if this treatment is useful. Indirect evidence through meta-analyses of secondary prevention of acute myocardial infarction indicate that beta-blockers, aspirin, and anticoagulants are effective in reducing mortality. Percutaneous transluminal coronary angioplasty has been used to ameliorate silent ischemia.[16] The assumption that treatments for silent ischemia are beneficial has the effect of biasing this analysis in favor of testing. Thus, the benefit of testing is likely to be even smaller if treatments for silent ischemia are not as efficacious as for symptomatic coronary artery disease.

3. The potential benefits of arrhythmia detection by ACM will be ignored.
4. The overall life expectancy will be used as the metric of comparisons.
5. Where there are no data, we will use data from symptomatic patients or non-MI patients as a proxy, modifying these values in sensitivity analyses to determine the relative importance of these estimates.
6. No distinction will be made in this analysis between thallium-201 scintigraphy performed with exercise or with dipyridamole, since the sensitivities and specificities

of these two methods are similar and both are noninvasive tests and do not have significant morbidities.

7. Cardiac catheterization is used as the gold-standard for diagnosis of CAD. Patients with positive noninvasive test results will undergo cardiac catheterization.

Description of the Decision Tree

This decision analysis compares the strategy of medical treatment without further testing and the strategies of using submaximal ETT, ACM, or thallium-201 scintigraphy for the detection of silent ischemia in asymptomatic post-MI patients. The four strategies are shown in the decision tree in figure II-1 and labeled as **ETT**, **ACM**, **THALLIUM**, and **NoTest**. The details of the decision tree are shown in figures II-2 through II-4.

The **NoTest** strategy, the bottom branch of the decision node, is linked to the subtree labeled **disease** (note that the node **disease** with the lower case "d" is different from the node **Disease** with the upper case "D") shown in figure II-2. The **disease** subtree models the prevalence of residual coronary artery disease in the study population and the likely distribution of number of diseased vessels labeled **lm** for left main disease, **3vd** for three vessel disease, **2vd** for two vessel disease, **1vd** for one vessel disease, and **nodis** for no residual disease. The life expectancies for each of the outcomes treated by medical therapy are estimated using the DEALE model (declining exponential approximation of life expectancy).[17]

The top three branches of the decision node in figure II-1 are the three non-invasive testing strategies of **ETT**, **ACM** and **THALLIUM**. These tests carry insignificant morbidities and mortalities and their complications will be ignored in this model. The testing strategies share similar downstream tree structures. The test outcomes and the events following test results are modeled identically, the only difference being the sensitivities and

specificities of the tests. The common subtree structure is labeled **Disease** shown in figure II-3. Similar to the **NoTest** strategy, the prevalence of residual coronary artery disease is modeled. The outcomes of the test are also modeled. True positive results are represented by the node labeled **+CAD+Tes**, false negative outcomes are represented by the node **+CAD-Tes**, false positive outcomes are represented by the node **-CAD+Tes**, and true negative outcomes are represented by the node **-CAD-Tes**. Patients with a positive test result (true positive or a false positive) will undergo cardiac catheterization. Patients without catheterization complications are shown in the **CathOK** subtree (figure II-4). Patients are grouped into 5 categories after catheterization: left main disease (**LM**), three vessel diseases (**3VD**), two vessel disease (**2VD**), one vessel disease (**1VD**), and no residual disease (**NoDis**). Patients with correctable left main or three vessel disease will undergo CABG surgery modeled by the **CABG** node. CABG outcomes are modeled by the **CABGDie** and **CABGOK** nodes where a value of 0 is assigned to CABG mortality. Uncorrectable lesions will continue to receive medical therapy. Two vessel disease will undergo angioplasty if the lesion is amenable to the procedure. Angioplasty is modeled by the **Angiopla** node where angioplasty complications (**AngioCx**) needing emergent CABG, successes (**AngiSucc**) and failures (**AngiFail**) are modeled. One vessel disease will receive medical therapy. Complications and successes of surgical interventions are modeled. Life expectancies of various outcomes are calculated.

Review of the Literature

The literature on the detection of silent ischemia and the description of the clinical spectrum among asymptomatic post-infarction patients is scanty. As discussed earlier in the assumptions section, in places where data are lacking for the decision analytic model, data from patients with painful ischemia and non-infarction will be used as proxy.

Prevalence of silent ischemia among post-infarction patients

Several studies have provided estimates on the frequency of silent ischemia among post-infarction patients. In a study of 12,500 post-infarction patients in Germany, only 680 patients (5.4%) were observed to have silent ischemia on ETT.[4] Using ETT, a number of smaller studies found the rate of silent ischemia to vary between 17 and 33%.[2,6] A number of studies using ACM reported rates of 30% and 33% among post-infarction patients.[14,18]

Prevalence of residual CAD among post-infarction patients

Given the fact that ETT or ACM are not perfect tests (approximately 70% sensitivity), the prevalence of silent ischemia detected by these methods must be adjusted to estimate the prevalence of residual CAD among asymptomatic patients. The prevalence of residual CAD is estimated by multiplying the prevalence of silent ischemia (20%) by 1.43 (100%/70%). Based on data given in the paragraph above, the range of residual CAD among post-infarction patients with silent ischemia varies between 7.7% and 47%.

Distribution of diseased vessels

The incidence and distribution of diseased vessels among patients with silent or painful ischemia has been found to be similar.[19,20] A number of studies applied coronary angiography soon after acute MI to determine the anatomy of the coronary lesions.[10,21,22,23,24,25,26] None of these studies provide information on the frequency of symptoms among the study population. As expected, there was considerable variability among studies. Weighted pooled estimates of the diseased vessels distribution were performed by extracting the frequency of diseased vessels distribution from each study and weighting according to the size of the study. There were a total of 1,266 patients in these 7 studies. The pooled probability of left main, 3 vessel disease, 2 vessel disease, and 1 vessel disease are 2%, 36%, 29%, and 33%, respectively.

Sensitivity and specificity of submaximal ETT, ACM, Thallium-201

A number of recent meta-analyses have been published on the sensitivity and specificity of thallium-201 scintigraphy and standard ETT, and these will be used as a proxy in our analysis. Given the lower level of exercise intensity, the sensitivity and specificity of the submaximal ETT probably are lower than for the standard tests. Current literature does not provide adequate data on the sensitivity and specificity of the ACM, especially among post-infarction patients. The few studies that are available suggest that the sensitivity and specificity of ACM is lower than that of ETT or thallium-201 scintigraphy. Sensitivity and specificity for the ACM used in this analysis were estimated by

pooling available studies.[27]

Estimates of the following probabilities and utilities were obtained from a published decision analysis on myocardial revascularization for chronic stable angina[28] (see Table II-1):

- Mortality and Morbidity of Angiography
- Probability of correctable disease
- Morbidity and Mortality of Angioplasty
- Morbidity and Mortality of CABG
- Mortality rates of various coronary artery diseases
- Efficacy of Angioplasty
- Efficacy of CABG

Utilities

Life expectancy will be used as the utility. Age related average annual mortality rates are derived from standard life tables. Near term deaths such as those from surgical procedures will be assigned a value of 0. Estimation of life expectancy will be made using the DEALE model.[17] The DEALE model allows one to estimate the life expectancy of an individual by summing up various mortality rates based on age, underlying disease, and co-morbidities. The mortality rates may be adjusted according to the benefit of the treatment.

Results

Analyses were performed using values shown in Table II-1. The results of using four different prevalence values of residual CAD are shown in Table II-2. A prevalence of 5% represents the low end of the clinical spectrum, 25% represents the baseline scenario, 50% anchors the high end of literature data, and 100% is included to estimate the maximum likely benefit of testing. For each prevalence value, a sensitivity analysis on age from 55 to 80 was performed.

For the baseline scenario of a 55 year old man with a prevalence of residual CAD of 25%, the expected utilities for the three testing strategies are close, 16.51 years for submaximal ETT, 16.48 years for ACM, and 16.51 years for Thallium-201 scintigraphy. Testing is better than no testing by at most 0.18 years. For an 80 year old man, the result is a toss-up; that is, there is hardly any difference among the strategies.

At a low prevalence of residual CAD of 5%, the benefit of doing any testing over no testing is negligible, 0.03 year (approximately 10 days gain in the life expectancy of 16.58 years for no testing) for a 55 year old man. This benefit maximizes at the prevalence of CAD of 100%, when the benefit of thallium-201 scintigraphy over no testing becomes 0.73 year (approximately 9 months gain in life expectancy of 15.41 years for no testing) for the same 55 year old man. However, the difference between the best test (Thallium) and the worst test (ACM) remains small (0.09 year, or approximately 1 month in a life expectancy of 16 years).

Increasing age for each of the assumptions about the

prevalence has the effect of decreasing overall life expectancy and narrowing the differences among strategies. At age of 80 years, the prevalence of residual CAD of 5% translates to no differences among any tests and no testing (all strategies have a life expectancy of 6.19 years). At the prevalence of CAD of 100%, the maximum benefit of testing over no testing is 0.09 years.

The values for sensitivity and specificity of the tests are uncertain for post-infarction silent ischemic patients. Since all three of the testing strategies are non-invasive and are identical with the exception of values used for sensitivity and specificity, we can perform sensitivity analyses by substituting 3 sets of values of sensitivity and specificity in these strategies. We could then examine the effect of varying the sensitivity and specificity of the tests by using three sets of hypothetical values and labelling them as Test A, Test B, and Test C. We will use 90% as values for sensitivity and specificity for Test A, 75% for Test B, and 60% for Test C. The results of this sensitivity analysis are shown in Table II-3. The biggest difference between the test with the highest sensitivity and specificity (Test A) and the test with the lowest sensitivity and specificity (Test C) was only 0.09 year (approximately 1 month) in a 55 year old with a prevalence of residual CAD of 50%. The relative differences among testing strategies also tend toward zero with age of 80.

Using the baseline values, differences among the strategies are small. The apparent lack of differences among the strategies and the small benefit from any of the tests are due to the relative low prevalence of residual CAD among silent ischemic post-

infarction patients, the distribution of number of diseased vessels (low percentage of left main), and the relatively low excess mortality rate of one and two vessel diseases. To determine when large benefits may be realized from testing, a scenario was created and shown in Table II-4. For a 55 year old man, a large benefit (a gain of life expectancy of 2.43 years) of testing over no testing is possible if the prevalence of residual CAD is high (50%), if the diseased vessels distribution is predominantly left main (50%) and 3 vessels (50%), and if the sensitivity and specificity of the test are high (90%). In this scenario, a test with high sensitivity and high specificity (test A) is better than a test with low sensitivity and low specificity (Test C) by 0.52 years. Sensitivity analysis with age shows that in this scenario, the large gain in life expectancy is smaller with advanced age but still substantial (0.54 years gain of life expectancy for an 80 year old man using a test of 90% sensitivity and specificity versus no testing).

Conclusions

Using baseline values, additional non-invasive testing with submaximal ETT, ACM, or thallium-201 scintigraphy among asymptomatic post-infarction patients provides moderate gains in life expectancy in a 55 year old man (approximately 4 months out of a life expectancy of 16 years). This gain decreases with age. Any of the tests is better than no further testing; there is only a marginal difference among the choices. Given the small differences among the three non-invasive tests, and in the absence of specific

indications, cost should be an important consideration in deciding the choice of the test. Adequate data on post-infarction silent ischemia are lacking. This decision analysis was performed with estimates and proxies of data from symptomatic patients and non-post-infarction patients.

Large gains in life expectancy (0.5 years or more) can be achieved only when the prevalence of residual CAD among silent ischemic patients is high, the distribution of diseased vessels is predominantly left main or three vessels, and the test has high sensitivity and specificity. Due to many other unknown variables in this group of patients, the precise estimations of these values can not be determined at this time. Several ongoing trials study the issues of silent ischemia: ASIST (Atenolol in Silent Ischemia Trial), ACIP (NHLBI - Asymptomatic Cardiac Ischemia Pilot), TIBET (Total Ischemic Burden European Trial). Data from these trials should add substantially to our knowledge of silent ischemia and may provide more reliable estimates for this decision analytic model. Until then, the conclusions from this analysis must be viewed as tentative.

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Table II-1.
Baseline probability and utility values used in decision analysis.

Prevalence of residual CAD in asymptomatic post MI patients	0.25
Among patients with residual CAD	
Prevalence of left main	0.02
Prevalence of 3 vessel disease	0.36
Prevalence of 2 vessel disease	0.29
Prevalence of 1 vessel disease	0.33
Test sensitivity	
Submaximal exercise test	0.80
Ambulatory Cardiac monitoring	0.71
Thallium scintigraphy	0.81
Test specificity	
Submaximal exercise test	0.75
Ambulatory Cardiac monitoring	0.67
Thallium scintigraphy	0.80
Probability of catheterization mortality	0.002
Angioplasty for 2 vessel disease	
Probability of angioplastiable lesion	0.5
Probability of mortality	0.009
Probability of complication requiring CABG	0.023
Probability of success	0.85
Efficacy of angioplasty in reducing mortality	0.80
Elective CABG mortality	0.028
Emergent CABG mortality	0.037
Efficacy of CABG in reducing mortality rate	
Probability of correctable 3 vessels disease	0.42
Left main disease	0.89
3 vessels disease	0.50
2 vessels disease	0.67
Average annual excess mortality rates	
Left main disease	0.128
3 vessels disease	0.022
2 vessels disease	0.014
1 vessel disease	0.012

Table II-2.

Results of analyses (life expectancy in years)

Prevalence of residual CAD = 0.05

Age	Exercise	ACM	Thallium	NoTest
55	16.61	16.60	16.61	16.58
60	14.24	14.32	14.24	14.22
65	11.97	11.97	11.97	11.97
70	9.78	9.78	9.78	9.77
75	7.78	7.78	7.78	7.78
80	6.19	6.19	6.19	6.19

Prevalence of residual CAD = 0.25

Age	Exercise	ACM	Thallium	NoTest
55	16.51	16.48	16.51	16.33
60	14.16	14.14	14.16	14.03
65	11.91	11.90	11.91	11.82
70	9.73	9.73	9.74	9.68
75	7.75	7.75	7.75	7.72
80	6.17	6.17	6.17	6.15

Prevalence of residual CAD = 0.5

Age	Exercise	ACM	Thallium	NoTest
55	16.38	16.34	16.39	16.02
60	14.06	14.02	14.06	13.80
65	11.83	11.81	11.84	11.65
70	9.68	9.66	9.68	9.56
75	7.71	7.70	7.71	7.64
80	6.14	6.14	6.14	6.10

Prevalence of residual CAD = 1.0

Age	Exercise	ACM	Thallium	NoTest
55	16.13	16.05	16.14	15.41
60	13.86	13.80	13.87	13.33
65	11.68	11.64	11.69	11.31
70	9.57	9.54	9.57	9.32
75	7.63	7.62	7.64	7.48
80	6.09	6.08	6.09	6.00

Table II-3.

Results of analyses (life expectancy in years):

Effect of varying sensitivity and specificity of tests

Test A	Test B	Test C
sens/spec = 0.9	sens/spec = 0.75	sens/spec = 0.6

Prevalence of residual CAD = 0.05

Age	Test A	Test B	Test C	NoTest
55	16.62	16.60	16.59	16.58
60	14.25	14.24	14.23	14.22
65	11.98	11.97	11.96	11.96
70	9.78	9.78	9.77	9.77
75	7.79	7.78	7.78	7.78
80	6.19	6.19	6.19	6.19

Prevalence of residual CAD = 0.25

Age	Test A	Test B	Test C	NoTest
55	16.53	16.51	16.48	16.33
60	14.18	14.16	14.14	14.03
65	11.92	11.91	11.91	11.82
70	9.74	9.73	9.73	9.68
75	7.76	7.75	7.75	7.72
80	6.17	6.17	6.17	6.15

Prevalence of residual CAD = 0.5

Age	Test A	Test B	Test C	NoTest
55	16.43	16.38	16.34	16.02
60	14.10	14.06	14.03	13.80
65	11.86	11.83	11.81	11.65
70	9.70	9.68	9.66	9.56
75	7.72	7.71	7.71	7.64
80	6.15	6.14	6.14	6.10

Table II-4.

Results of analyses (life expectancy in years):

One scenario that produce big differences among strategies.

probability of residual CAD = 0.5

probability of Left Main = 0.5
probability of three vessels disease = 0.5

Test-A sensitivity and specificity = 0.9
Test-B sensitivity and specificity = 0.75
Test-C sensitivity and specificity = 0.6

Age	Test-A	Test-B	Test-C	NoTest
55	15.74	15.33	14.92	13.31
60	13.55	13.23	12.90	11.60
65	11.45	11.19	10.94	9.93
70	9.40	9.21	9.02	8.27
75	7.52	7.38	7.25	6.73
80	6.00	5.91	5.82	5.46

Figure II-1

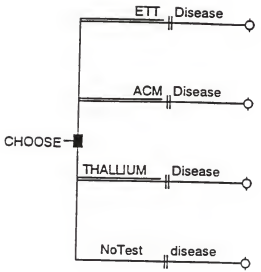
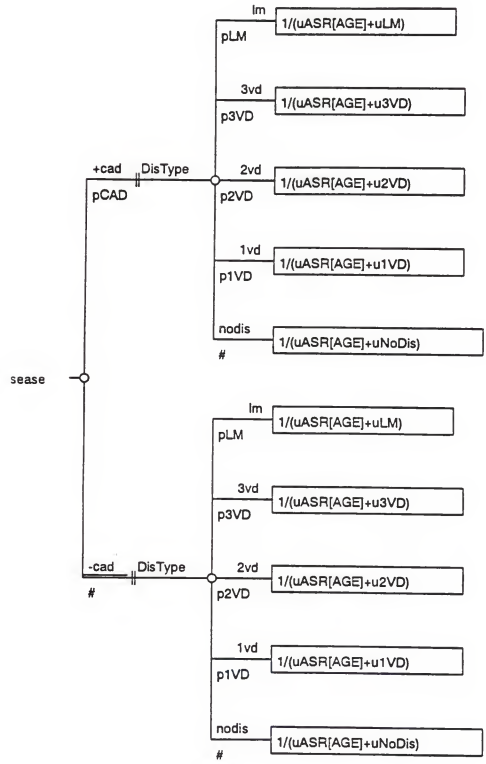

ETT
Disease
ACM
Disease
CHOOSE
THALLIUM
Disease
NoTest
disease

Figure II-2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1/(uASR[AGE]+uLM)
pLM
3vd
1/(uASR[AGE]+u3VD)
p3VD
+cad
DisType
2vd
1/(uASR[AGE]+u2VD)
pCAD
p2VD
1vd
1/(uASR[AGE]+u1VD)
p1VD
nodis
1/(uASR[AGE]+uNoDis)
#
sease
lm
1/(uASR[AGE]+uLM)
pLM
3vd
1/(uASR[AGE]+u3VD)
p3VD
-cad
DisType
2vd
1/(uASR[AGE]+u2VD)
#
p2VD
1vd
1/(uASR[AGE]+u1VD)
p1VD
nodis
1/(uASR[AGE]+uNoDis)
#

Figure II-3

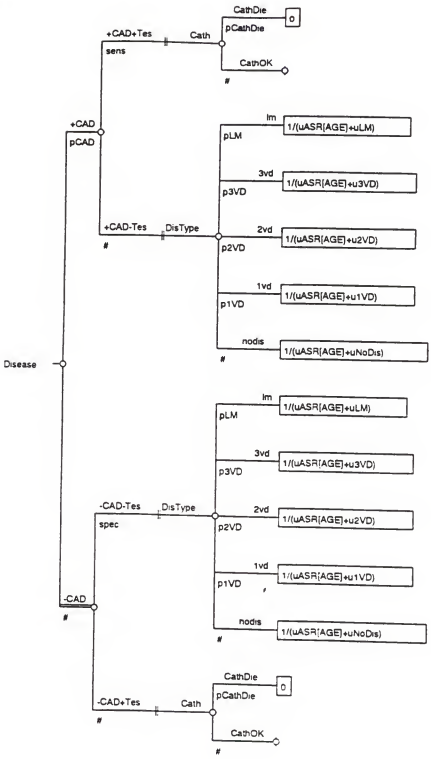
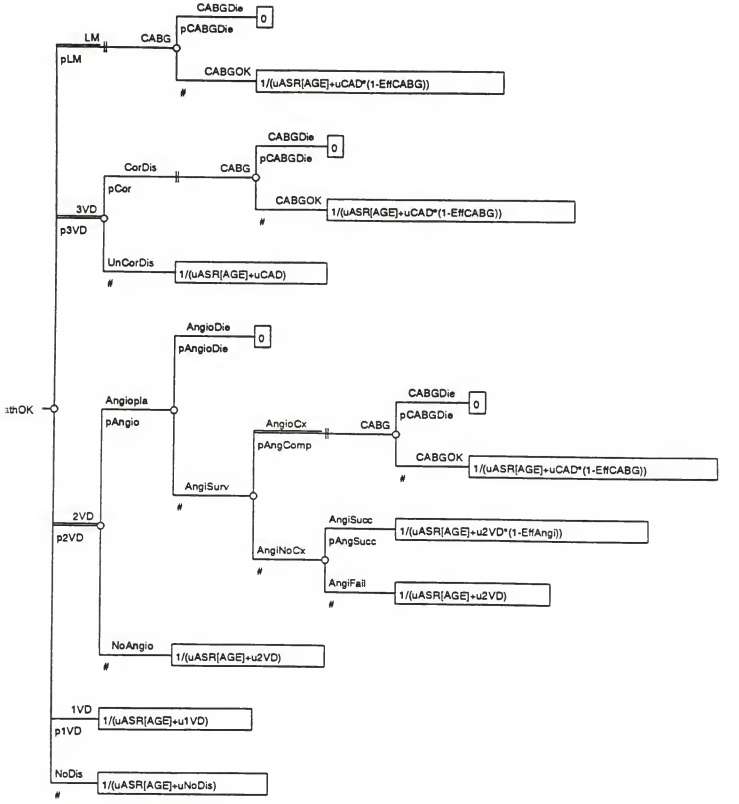

Disease
+CAD
pCAD
+CAD+Tes
sens
Cath
CathDie
0
pCathDie
CathOK
#
+CAD-Tes
DisType
lm
pLM
1/(uASR[AGE]+uLM)
3vd
p3VD
1/(uASR[AGE]+u3VD)
2vd
p2VD
1/(uASR[AGE]+u2VD)
1vd
p1VD
1/(uASR[AGE]+u1VD)
nodis
1/(uASR[AGE]+uNoDis)
-CAD
-CAD-Tes
spec
-CAD+Tes

Figure II-4


CABGDie
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pCABGDie
LM
CABG
pLM
CABGOK
1/(uASR[AGE]+uCAD*(1-EffCABG))
#
CABGDie
0
pCABGDie
CorDis
CABG
pCor
CABGOK
1/(uASR[AGE]+uCAD*(1-EffCABG))
3VD
#
p3VD
UnCorDis
1/(uASR[AGE]+uCAD)
#
AngioDie
0
pAngioDie
CABGDie
0
pCABGDie
AngioCx
CABG
pAngComp
CABGOK
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pAngSucc
AngiNoCx
#
AngiFail
1/(uASR[AGE]+u2VD)
#
2VD
p2VD
NoAngio
1/(uASR[AGE]+u2VD)
#
1VD
1/(uASR[AGE]+u1VD)
p1VD
NoDis
1/(uASR[AGE]+uNoDis)
#

APPENDIX IIA. Description of the abbreviations used in the decision tree of ACM for the diagnosis of silent ischemia among post-MI patients.

This decision tree was implemented with features and notations of DMAKER 7.0[29] (a decision analysis software for IBM compatible microcomputers).

Label node provides a means of identifying a point in the decision tree that uses subtree structures. It may be considered to be equivalent to chance node or decision node with a single branch.

General abbreviations:
CAD - coronary artery disease
CABG - coronary artery bypass graft surgery

The letter in the bracket following the node-name denotes node-type:
D - decision node C - chance node
L - label node T - terminal node

Node Name	Node Type	Description
CHOOSE	[D]	- Top level decision node considering the three strategies of ACM, THALLIUM, and NoTest.
ETT	[L]	- Submaximal exercise testing.
ACM	[L]	- Ambulatory Cardiac Monitoring strategy.
THALLIUM	[L]	- Exercise Thallium-201 Scintigraphy.
NoTest	[C]	- Expectant management strategy without further testing.
Disease	[C]	- A subtree used by both ACM and Thallium strategies. This chance node models the prevalence of CAD.
disease	[C]	- Similar to above but used by NoTest strategy.
+CAD	[C]	- Patients with CAD.
-CAD	[C]	- Patients without CAD.
+cad	[C]	- Similar to +CAD, but used by NoTest strategy.
-cad	[C]	- Similar to -CAD, but used by NoTest strategy.
+CAD+Tes	[L]	- Patients with CAD and positive tests. (True Positive)
+CAD-Tes	[L]	- Patients with CAD and negative tests. (False Negative)
-CAD+Tes	[L]	- Patients without CAD and positive tests. (False Positive)
-CAD-Tes	[L]	- Patients without CAD and negative tests. (True Negative)
Cath	[L]	- Cardiac catheterization.
CathDie	[T]	- Cardiac catheterization related mortality.
CathOK	[C]	- Survived catheterization.
3VDLM	[C]	- Left main or 3 vessels disease (from testing strategies).
1VD2VD	[T]	- 1 or 2 vessels disease (from testing strategies).
NoDis	[T]	- No residual disease (from testing strategies).
DisType	[C]	- (Disease Type) A subtree used to model the vessels distribution of CAD of no cath branches.
3vdlm	[T]	- Left main or 3 vessels disease (from no cath branches).
1vd2vd	[T]	- 1 or 2 vessels disease (from no cath branches).
nodis	[T]	- No residual disease (from no cath branches).
CorDis	[L]	- Surgery correctable disease, goes to CABG.
UnCorDis	[T]	- Uncorrectable disease.
CABG	[C]	- Coronary artery bypass graft surgery.

CABDDie [T] - CABG related mortality.
CABGOK [T] - Survived CABG surgery.
NoAngio [T] - Lesions not amendable to angioplasty.
AngioDie [T] - Mortality directly related to angioplasty.
AngiSurv [C] - Survived angioplasty.
AngioCx [L] - Complications arising during angioplasty, require emergency CABG.
AngiNoCx [C] - No complications from angioplasty.
AngiSucc [T] - Successful angioplasty.
AngiFail [T] - Unsuccessful angioplasty but without complications.

Probability and Utility abbreviations:

pCAD	- probability of CAD
sens	- sensitivity of the test
spec	- specificity of the test
pCathDie	- probability cardiac catheterization associated deaths
pLM	- probability of left main disease
p3VD	- probability of 3 vessel disease
p2VD	- probability of 2 vessels disease
p1VD	- probability of 1 vessel disease
pCor	- probability of correctable disease
pCABGDie	- probability of CABG surgery mortality
pAngio	- probability of angioplastiable lesions
pAngioDie	- probability of angioplasty mortality
pAngComp	- probability of angioplasty complications
pAngSucc	- probability of successful angioplasty
#	- the residual probability of the chance node
uASR	- averaged annual mortality rate based on age, sex, race
uLM	- excess mortality rate of left main disease medically treated
u3VD	- excess mortality rate of three vessels disease medically treated
u2VD	- excess mortality rate of two vessels disease medically treated
u1VD	- excess mortality rate of one vessel disease medically treated
uNoDis	- excess mortality rate of post-MI patients without residual disease
EffAngi	- efficacy of angioplasty in reducing excess mortality of 2 vessels disease
EffLM	- efficacy of CABG in reducing exess mortality of left main disease
Eff3VD	- efficacy of CABG in reducing excess mortality of 3 vessels disease
Eff2VD	- efficacy of CABG in reducing excess mortality of 2 vessels disease

EFFECTIVENESS OF AMBULATORY CARDIAC MONITORING: EVALUATION OF ANTIARRHYTHMIC AGENTS

Introduction

Our previous report in part considered the evidence for the effectiveness of ambulatory cardiac monitoring (ACM) in the assessment of the efficacy of antiarrhythmic therapy for a number of clinical conditions involving cardiac arrhythmias. Current information about the unpredictable response to antiarrhythmic agents suggests that the only unequivocal indication for ACM appears to be as part of research to find efficacious and safe antiarrhythmic agents. Findings of our meta-analyses questioned not only the use of ACM in the selection and evaluation of antiarrhythmic drugs, but also the use of the drugs themselves to control cardiac arrhythmias and to reduce the risk of cardiac death in some patients post-infarction. Concerns about efficacy and safety were especially expressed for the Type I antiarrhythmic agents post-infarction. Further review of the literature has led us, in this second phase of evaluation of ACM, to limit our analysis to post-infarction patients with malignant arrhythmias. Malignant arrhythmias are defined as ventricular tachycardia or ventricular fibrillation with organic heart disease and a markedly increased risk of sudden cardiac death. For other types of arrhythmias (potentially malignant and benign), the lack of demonstrated effective and safe treatment to control the

arrhythmias makes treatment and therefore routine ambulatory monitoring for suppression of arrhythmias of questionable utility.[1-3]

Traditional approaches to the management of patients with malignant ventricular tachyarrhythmias such as ventricular tachycardia and ventricular fibrillations[4] include the use of ambulatory electrocardiographic monitoring[5] to document the presence of ventricular arrhythmias, and suppression of any demonstrated arrhythmias with one or more of the antiarrhythmic drugs.[6] The suppression of any ventricular arrhythmia demonstrated during ambulatory cardiac monitoring has been used as an endpoint indicating adequate response to antiarrhythmic drug treatment.

More recently electrophysiologic testing (EPS) has been introduced as an alternative to ACM. Despite the expense and complexity of electrophysiologic studies, the preponderance of antiarrhythmic therapy is currently selected using this method of testing.[1] Results from a number of studies indicate that EPS may be better able to predict which antiarrhythmic agent will be effective, but it is expensive, potentially poses a greater risk to patients, and according to some reports identifies effective antiarrhythmic drugs in fewer patients than traditional ACM.[1]

Although several studies have compared ACM to EPS, the majority are of limited power because of small sample sizes, and are subject to bias because of general lack of randomization and blinding.[4,7-11] However, most of these studies suggest that more patients qualify for EPS than ACM and that EPS more accurately

predicts clinical outcome. In a small study by Mitchell and colleagues,[12] 57 patients who qualified for both testing methods were randomized to one or the other, given antiarrhythmic therapy, and followed for recurrence of arrhythmias, acute myocardial infarction, total mortality, and number of drug trials and hospital days required to select therapy. Although the conclusions drawn from this study are limited by the sample size, this study does provide estimates that we have found very useful for illustration in the decision analysis models proposed here. The ESVEM Study (Electrophysiologic Study Versus Electrocardiographic Monitoring for Selection of Antiarrhythmic Therapy of Ventricular Tachyarrhythmias)[13] currently underway at 14 sites compares EPS to ACM for drug selection in a group of approximately 500 subjects. Results of this randomized controlled trial are expected soon, and we hope will provide better information about many of the questions raised in our present report.

The use of ACM or EPS to select antiarrhythmic agents is predicated on the belief that the use of such agents results in improved patient outcome. Current evidence for the effectiveness of antiarrhythmic therapy for reducing cardiac or overall mortality is inconclusive. A number of studies suggest that control of complex ventricular ectopic activity based on a noninvasive evaluation (ACM) or the suppression of their provocation by programmed electrical stimulation (EPS) is associated with improved survival in high risk patients.[6,9,14-17] This relationship needs further evaluation.

The question addressed here we have posed as: Should ACM or electrophysiologic stimulation (EPS) be used to test the effectiveness of antiarrhythmic agents? The approach of our current work relies to a greater extent on decision analytic techniques. Using the currently existing data, we have analyzed this problem in terms of the following questions:

1. What are the alternative methods of antiarrhythmic selection and evaluation?
2. What are the relevant outcomes?
3. What factors are important in defining those outcomes?
4. Which variables are most important in determining the preferred method of drug selection and evaluation?

Methods

This analysis uses a decision tree model to evaluate the role of ambulatory cardiac monitoring in the selection and evaluation of antiarrhythmic agents in patients with malignant arrhythmias. Decision analysis affords a systematic approach to evaluation of a clinical problem and helps clarify the logic underlying clinicans' decisions. The intention is not to replace clinical experience, but rather to provide a framework or way of thinking which can help maximize the value of experience and scientific knowledge. A decision analysis begins by defining the problem and the potential course of action or alternatives. A decision tree illustrates the problem, the range of solutions, and their outcomes. It identifies which estimates or probabilities of events are needed, and the outcomes that are important. The exercise of modeling a problem using decision analysis can help organize complicated clinical dilemmas which often have competing and disparate objectives and outcomes. In addition to helping guide decisions, this type of analysis can guide future research by identifying critical areas where additional data are needed from clinical trials.

The models developed for this analysis to assess the role of ambulatory cardiac monitoring in the evaluation of antiarrhythmic agents consider three alternatives:

1. Ambulatory Cardiac Monitoring alone;
2. Ambulatory Cardiac Monitoring to select an agent followed by exercise testing to further assess drug effectiveness;

3. Electrophysiologic Studies (EPS) or Programmed Ventricular Stimulation.

The three alternative methods have certain advantages and disadvantages based on clinical outcomes and resource utilization. The purpose of this analysis is to determine the optimal approach that yields the most accurate predictions of drug efficacy, rates of arrhythmia recurrence, of acute myocardial infarction, or of mortality, and resource utilization outcomes. As complete data are not yet available, decision analysis can be helpful in identifying the best alternative given currently available data, and in identifying critical areas where more accurate information is needed.

Our general model begins by choosing an evaluation method and considers three main steps (Figure III-1a). Step I identifies the proportion of patients who qualify (Q+), or fail to qualify (Q-) for the particular evaluation method. Estimates for the probability of qualifying, or of being able to undergo agent selection, are based on available published reports of direct comparisons of these methods in clinical trials (Table III-1). For patients who qualify, Step II considers selection of antiarrhythmic agents by sequentially testing a series of agents until one is identifed that suppresses the arrhythmia (S+). Patients who do not qualify for the evaluation method, and those who qualify but go through the entire list of antiarrhythmic agents without identifying an effective agent (S-), are given amiodarone. Amiodarone is often used as the last alternative antiarrhythmic agent (rather than earlier on in

the series) because of its frequent, severe toxicity.[18] Step III involves identification and valuation of relevant outcomes.

This basic model can be extended so that patients who do not qualify for the first testing method proceed to try an alternative method of selection. Patients who fail to qualify for ACM or ACM/Exercise Testing go on to try Electrophysiologic Studies. Those who initially do not qualify for EPS, go on to have ACM.

See Appendix IIIA for a list of abbreviations used in the decision models.

STEP 1 : Qualifying

Several studies provide estimates of patient eligibility for the three alternative evaluation procedures. These estimates are summarized in Table III-1.

Branch I: Ambulatory Cardiac Monitoring

Only if the patient demonstrates 10-30 VPDs/hr during monitoring can ACM be used to select an agent. This range represents 50-67% of patients with malignant arrhythmias.[12,19,21,22] The estimate used in the Base Case Analysis for ACM qualification is 59%.

Branch II: ACM/Exercise Testing

In addition to the criteria for use of ACM, the patient must be able to undergo exercise testing. Physical limitations prevent some patients from undergoing this part of the examination. In the study by Mitchell and colleagues,[12] 88% of patients were able to complete the baseline exercise test, 5% were able to exercise on a

supine bicycle ergometer, leaving 7% for whom graded exercise assessment was contraindicated. Although the combination of ACM/Exercise Testing can be useful in identifying drug-associated aggravation of arrhythmias, it can be very expensive because of the extended hospitalization needed for drug/dose identification.

Branch III: Electrophysiologic Studies

EPS is the most commonly used method to evaluate drugs in patients with malignant arrhythmias. It is thought to be sensitive, reproducible, and accurate for predicting long-term outcomes of interest and good for detecting adverse effects of drugs.[20] However, it is impractical for testing the full dose range and can be very expensive for drug resistant patients.

To qualify for EPS. patients are taken off all antiarrhythmic agents and undergo programmed ventricular stimulation to see whether arrhythmias can be induced. Those who have arrhythmias induced representative of their clinical arrhythmia, approximately 80% of patients,[12,20,21] can proceed to testing the effectiveness of antiarrhythmic drugs (Q EPS+).

Step 2 : Agent Selection

Branch I: Ambulatory Cardiac Monitoring

After the monitoring period, drugs are given and monitoring continued to see whether the previously documented arrhythmia is suppressed. If it is, then the drug is selected (S+), if not, then the patient is given some last alternative drug (S-). Significant random variation in the identification of arrhythmias using ACM

requires that the suppression of arrhythmias be carefully counted and that the suppression be a dramatic reduction or complete suppression as follows (see Table III-2):

50-80% decrease in VPD frequency

80-90% decrease in paired VPDs

90-100% decrease in runs of sustained tachyarrhythmia

Although formal studies adhere to these criteria,[1,6,12,13] clinicians in practice may not, and this would affect the utility of the results of this analysis for clinical practice.

It is generally possible to select an effective agent for all patients initially using Ambulatory Cardiac Monitoring; however, some patients require a change in drug at some later time. Mitchell and colleagues[12] report 38% of patients switching to another drug, with 24% ending up on amiodarone.

Branch II: ACM/Exercise Testing

Exercise Testing is useful for provoking arrhythmias on drugs judged to be efficacious by ACM.[23] Additionally, Exercise Testing can reveal drug-associated aggravation of ventricular arrhythmias. These pro-arrhythmic effects occur in 5-15% of patients, and vary by agent. This effect is incorporated into the model by reducing the probability of selecting an effective agent by 10%.

Branch III: Electrophysiologic Studies

Antiarrhythmic agents are considered effective using EPS testing when there is conversion of inducible sustained ventricular tachycardia to unsustained VT or no inducible VT (S+). In this model EPS identifies antiarrhythmic agents in approximately half of

patients. The remaining patients (S-) receive amiodarone whether or not it successfully blocks the induced arrhythmia. To evaluate drug effectiveness in follow-up using EPS, it is necessary to hospitalize the patient.

Step 3: Outcomes

Outcomes of interest are the same for each branch and include:

Clinical Health Outcomes

Number for whom an agent can be selected

Number remaining on initially selected agent

Rate of drug-associated aggravation of the arrhythmia

Arrhythmia recurrence rate

Rate of acute myocardial infarction

Death rate

Resource Utilization Outcomes

Number of hospital days

Number of trials needed to select drugs

Costs for the evaluation

Overall costs

Not all outcomes will be considered in this analysis. Specifically, we will consider the proportion of patients for whom an agent can be selected, and the rates of drug-associated aggravation of the arrhythmia, of recurrence of the arrhythmia, and the number of hospital days and trials needed for drug selection. We will not explicitly evaluate other clinical health and resource utilization outcomes, but will discuss the potential impact the alternative

testing methods can be expected to have on these outcomes.

Mitchell and colleagues[12] reported information on clinical health and resource utilization outcomes. Table III-3 presents estimates for successful drug selection, acute myocardial infarction, and overall mortality rates, as well as the number of drug trials and hospital days required for evaluation and drug selection for ACM and EPS. In our analysis we assumed, when used alone, ACM required 20 days and EPS 33 days as reported. For the sequential testing, we assumed ACM or ACM/Exercise Testing followed by EPS would require 2 days to fail to qualify for ACM or ACM/Ex and 33 days for EPS (35 days total). EPS followed by ACM or ACM/Exercise Testing would require one day to fail to qualify for EPS plus 20 days for ACM or ACM/Ex (21 days total). For the paths S-, we assumed subjects required a maximum amount of time in hospital for drug selection and used the mean plus one standard deviation for our estimates. This resulted in estimates of 35 days for S ACM- or S ACM/Ex-, 56 days for S ACM-EPS- or S ACM/Ex-EPS-, 59 days for S EPS-, and 36 days for S EPS-ACM-.

Estimates were made of the number of drug trials required for agent selection as follows: 3.2 for ACM and ACM/Ex and 5.5 drug trials for EPS are assumed for patients who have agents selected using any of the methods. For the paths S-, where patients cannot have agents selected, we assumed a greater number of drug trials were required, the mean plus one standard deviation. This resulted in an estimate of 5.0 drug trials for S ACM- or S ACM/Ex-, and 8.3 for S EPS-. For subjects who do not qualify for any testing method,

we assumed there would be one drug trial when these patients would receive amiodarone.

Base Case Analysis

The Base Case Analysis uses central estimates for probabilities of events and utilities for outcomes. In instances where only one estimate is available in the literature, it is used. When multiple estimates are available, generally the mean is taken for the Base Case Estimate.

Sensitivity Analysis

Decision analysis frequently is typified as making decisions under conditions of uncertainty. The limited data available for many of the estimates needed in this analysis illustrates this point. Faced with limited data and the ensuing uncertainty, a sensitivity analysis is performed to determine the effects of changes in the various probabilities on the outcome of the analysis. When multiple estimates of a value are available from published reports, the extremes can be used as high and low estimates in the sensitivity analysis. When only one estimate is reported, threshold analysis is performed where the values are progressively increased or decreased until the outcome of the analysis is changed.

MODEL I

The first model we consider is a simplified approach comparing

the three alternative testing methods for selection and evaluation of antiarrhythmic agents (Figure III-1). It evaluates the utility of each testing method in isolation, i.e., it considers what happens when all patients are evaluated by one method only. The basic outline of Model I is represented in Figure III-1 for ease of illustration. Points where probabilities and utilities are needed are identified. It is assumed that at each point where a minus (-) sign is found (e.g., S ACM-; Q ACM-) patients will be given amiodarone.

Probabilities

For each testing method, either Branch I, II, or III, probabilities are estimated for the number of patients who qualify using the particular testing method. Estimates are derived from study results summarized in Table III-1. Of the patients who qualify for the method, probabilities are again estimated of whether or not an antiarrhythmic agent can be selected that will "successfully" control or suppress the arrhythmia. These estimates are derived from studies summarized in Table III-3. Patients for whom no agent can be selected are generally given a last alternative, amiodarone. Because this model only considers the results of one testing method in isolation, it is assumed that patients who do not qualify are also given the last alternative, amiodarone.

Utilities

The first outcome of interest is the ability of the testing method to select antiarrhythmic agents that suppress, or prevent induction of, VPDs. Thus, the utility of S ACM+ or S ACM/Ex+ or S EPS+ (the points indicating successful agent selection) is set at 1.0 and the utility of all other branches at 0.0. This analysis allows us to identify which method can most often identify an agent capable of suppressing or preventing induction of arrhythmias in patients with malignant arrhythmias. Use of this outcome, however, may be misleading in that it assumes a relationship between the identification of a "successful" agent and the ultimate goals of minimizing recurrence of arrhythmic activity, myocardial infarction, and mortality. It also does not take into account costs in terms of initial hospitalization, number of drug trials, need for re-hospitalization, costs of treating side effects of treatment, and many other considerations. Model I, though simple, is useful to illustrate some points about this analysis.

MODEL II

The extended model depicted in Figure III-2a considers what happens when patients who do not qualify for the first testing method undergo evaluation by an alternative method. For example, in Branches I and II, patients who do not have sufficient VPD activity to qualify for selection of antiarrhythmic therapy using Ambulatory Cardiac Monitoring can undergo EPS. Similarly in Branch III, patients who cannot have an arrhythmia induced representative of

their clinical arrhythmia by EPS can undergo ACM with or without Exercise Testing. The purpose of this extension is to try to better understand the relative value of alternative sequencing of these testing methods. This model is analyzed using several alternative outcome measures including proportion of patients for whom an agent can successfully be selected, proportion of patients recurrence free, number of hospital days and number of drug trials required to select therapy.

Results

MODEL I

In Figure III-1a, Base Case estimates for successful drug selection are substituted for the needed probabilities and utilities. Expected utilities for each branch are also calculated and presented.

Base Case Analysis

When the decision tree is analyzed, Branches I and III representing the use of Ambulatory Cardiac Monitoring alone and EPS respectively, result in virtually identical expected utilities (0.45 and 0.44). Even though estimates of the proportion of patients who qualify for testing by EPS are much higher than for ACM (0.81 versus 0.59), fewer patients are able to have a "successful" drug selected using EPS (0.54 versus 0.76). The decision tree format helps to illustrate the impact of these probabilities on the proportion of patients assigned an agent selected by each testing method. The differences between ACM and ACM/Exercise Testing are greater than ACM versus EPS due to the reduced proportion of patients qualifying because they cannot tolerate exercise testing (7%), and because some agents are not selected (10%) when exercise testing reveals drug-associated aggravation of the ventricular arrhythmia. It is important in considering the comparison of these methods to try to estimate the benefit of Exercise Testing's ability to identify pro-arrhythmic effects. Handling the issue of pro-arrhythmic effects is challenging. On the one hand, identification of these effects is a

benefit as it most likely helps identify a potentially serious side effect of antiarrhythmic therapy and should help avoid unnecessary mortality. However, by so identifying such effects, Exercise Testing may reduce the number of patients for whom an agent can be selected. Although some studies have estimated rates of drug-associated aggravation of arrhythmias, these studies do not report how such identification affects the rate of "successful" drug selection. This is an important piece of information not available for this analysis. This simple model assumes that identification of pro-arrhythmic effects results in a decrease in the proportion of patients for whom an agent can be selected. Thus, this "benefit" has a negative impact on the estimates of outcomes for this testing method when one considers ability to select an agent as the outcome of interest.

Figure III-1b presents the results when the outcome "proportion of patients remaining recurrence free" is considered. Here, EPS provides the greatest expected utility compared with Ambulatory Cardiac Monitoring or ACM/Exercise Testing (0.75 versus 0.52 or 0.51).

Sensitivity Analysis

Results of the sensitivity analysis for Model I are reported in Table III-4. Using the Base Case Estimates of probabilities and utilities, Branch I, ACM alone, provided the greatest expected utility (ACM 0.45 versus EPS 0.44 versus ACM/Ex 0.38). A threshold analysis was performed, changing the probability of qualifying for

EPS or ACM/Ex, or of selecting agents using these methods, until an estimate was found that would make the expected utility of the alternative method equal to that of ACM alone. More extreme values would change the results of the decision analysis to favor the alternatives. Table III-4 reports the Base Case Estimates used, and the estimated threshold value for each probability. The threshold values for Qualify EPS+ or Select EPS+ are not very different from the Base Case values, while the threshold values for Qualify ACM/Ex+ or Select ACM/Ex+ are considerably greater than the Base Case values. Although the highest estimate from published reports for Qualify EPS+ (0.82) is still lower than the threshold value, it is very close and would not be an unlikely possibility.

MODEL II

Figure III-2 illustrates the extended model that considers the relative value of alternative sequencing methods for antiarrhythmic agent testing. Figure III-2 indicates decision points and points where probabilities and utilities are needed. The primary difference in the structure of this model begins when patients fail to qualify for the first testing method. In Branches I and II, patients who fail to qualify for ACM or ACM/Exercise Testing are next tested using EPS. In Branch III, EPS failures are next tested using ACM.

Probabilities

In Figure III-2a the probabilities of events are substituted.

In this model, it is assumed that the probabilities of qualifying for each testing method are independent of the order of testing. In other words, the probability of qualifying for EPS is the same (0.81) if it is given first or to patients failing to qualify for ACM. A similar assumption is made for estimates of successful selection of agents by the various methods. Although we expect that patients who qualify for a method are different from those who fail to qualify for that method and that final drug selection and outcomes will likely be different for these two groups, information on this is not available, so we were forced to use these simplifying assumptions. These assumptions need to be tested in clinical trials.

Utilities

Using utilities of 1.0 if agents were selected and 0.0 otherwise, as in Model I, has limited usefulness. Data on the outcomes of patients who had antiarrhythmic agents selected using the alternative testing methods are extremely limited. Reasonably good estimates are available about how many patients can have agents selected, but little information has been reported about which agents are chosen, and even less has been reported about the ensuing long-term outcomes of interest such as recurrence of symptomatic arrhythmias, myocardial infarction, and mortality. Model II analysis will begin using the same outcome of successful drug selection as Model I for comparison, but will also include the outcomes of VPD recurrence and resource utilization outcomes.

Although Mitchell[12] reported rates of sudden death and total mortality for the two selection methods, estimates were not reported separately for subjects who had drugs successfully selected and those who were given amiodarone. Thus, we were unable to use these outcomes in evaluating this model.

Base Case Analysis

Selection of antiarrhythmic agents

Ambulatory Cardiac Monitoring provides the greatest expected utility (0.63 ACM versus 0.58 ACM/Exercise Testing or 0.52 EPS) when one considers the selection of antiarrhythmic agents (Figure III-2b).

Proportion of patients recurrence free

Figure III-2c presents estimates indicating EPS maximizes expected utility compared with ACM or ACM/Exercise Testing (0.76 EPS versus 0.64 ACM/Ex and 0.63 ACM) when the outcome "proportion of patients recurrence free" is considered.

Resource utilization

Using number of hospital days as the outcome resulted in an expected utility of 26 days for ACM, 26.75 days for ACM/Exercise Testing, and 31 days for EPS (Figure III-2d). This provides a rough estimate of the total number of days required for each alternative testing path and identifies ACM as the alternative minimizing the number of hospital days required for antiarrhythmic drug selection and evaluation.

Figure III-2e considers the number of drug trials required to find a successful agent for each testing method. Branch I, beginning with ACM alone required the fewest expected number of drug trials (4.48) followed by ACM/Ex (4.63) and EPS (5.98).

Sensitivity Analysis

A sensitivity analysis for Model II considered the threshold values required to make ACM/Exercise Testing and EPS equivalent in Expected Utility to ACM (Table III-5). No threshold value could be found for the probability of qualifying for EPS to make Branch III equivalent to Branch I. The threshold value for the probability of qualifying for ACM/Exercise Testing is estimated at 0.84 (versus 0.55 Base Case). The probability of selecting an agent would have to increase from 0.54 to 0.67 for EPS and from 0.55 to 0.90 for ACM/Ex to make those branches equivalent to ACM alone. All of these estimates are considerably higher than any of the values used to derive the Base Case estimates.

Discussion

Electrophysiologic Studies are often recommended as the method of choice for selection of antiarrhythmic agents because a larger proportion of patients qualify for this testing method than for ACM (0.81 versus 0.59). As Model I very simply illustrates, however, patients have essentially the same probability of having an agent identified using either testing method because of the lower rate of agent selection by EPS once patients have qualified for testing (0.54 versus 0.76). In evaluating testing methods, it is important to consider both the rates of qualifying and selecting, and to consider whether different patients are being included by the two methods. Although roughly the same proportion of patients end up with an agent selected using the alternative methods, it is likely that the different methods will select different sets of patients. In other words, the 45% that have agents selected using ACM are not the same as the 44% using EPS. It is important to understand how these patients differ and what their long-term responses to therapy are.

The analysis of model II considers what happens when patients fail to qualify for one method of selection, and evaluation is attempted with the alternative method. Interpretation of these results is difficult as the optimal sequence of test trials differs by the outcome measure under consideration. The sequence in Branch I of ACM followed by EPS provided the greatest proportion of subjects for whom an agent could successfully be selected. However, the sequence in Branch III of EPS followed by ACM resulted

in the greatest proportion of patients remaining recurrence free. Both successful agent selection and remaining recurrence free are short term outcomes of interest in this clinical situation and are important in predicting long term outcomes. It may be that these alternative sequencing schemes maximize different aspects of patient response, or that the problem lies with the definition of "successful agent selection." Data relating rate of successful agent selection to longterm patient outcomes are lacking. With respect to Branch II that considers the use of Exercise, the outcome "successful agent selection" posed other difficulties in interpretation. Clinically one would expect that identification of proarrhythmic effects by Exercise testing would help reduce excess mortality and be of benefit. However, by identifying proarrhythmic effects, Exercise testing eliminates some agents that might otherwise have contributed to a higher successful selection rate. This apparent contradiction needs attention.

The estimates of effectiveness measured as proportion of patients recurrence free, and the estimates of resource utilization as number of hospital days or drug trials can be combined to make cost-effectiveness comparisons of the alternative testing methods and sequences. Again, let us emphasize the limitations of any conclusions when we make such comparisons. The two resource utilization outcomes, number of hospital days and drug trials, consistently identified the sequence in Branch I of ACM followed by EPS as the one minimizing resource expenditure. Further, our model suggests that considering these outcomes, the strategy of EPS

followed by Ambulatory Cardiac Monitoring in patients who do not qualify for EPS (Branch III) is likely to provide a greater expected utility than the strategy of ACM followed by EPS, but at additional health resource costs.

Although it was possible to create a decision analysis model that could be very useful for assessment of the use of Ambulatory Cardiac Monitoring in the selection and evaluation of antiarrhythmic therapy, the limited data available constrained our analysis. In particular, the model would be most useful if it were possible to infer a relationship between selection of agents using the alternative methods and the long-term clinical outcomes of morbidity and mortality. With respect to the ACM/Exercise Testing strategy, it is important to determine what impact identification of pro-arrhythmic effects have on overall patient outcome. Many investigators cite this benefit as being very valuable; however, data estimating its impact on morbidity, mortality and costs of care are lacking.

It is also important to consider that Ambulatory Cardiac Monitoring evaluates the effect of antiarrhythmic therapy on spontaneously occurring arrhythmias while Electrophysiologic studies evaluate the agent's ability to block artifical induction of arrhythmias.[24] If these two testing methods are providing information on different mechanisms of drug efficacy, it may be important to use both methods. Data currently available in the literature do not address this issue.

Because the available data are extremely limited, conclusions

cannot be drawn with any considerable degree of confidence; however, development of this model does help to identify areas of particular concern and need for future research. The most important area where data are lacking concerns the relationship between drug selection and long-term outcomes. A number of studies estimate the proportion of patients with malignant arrhythmias that can have antiarrhythmic agents selected using either ACM or EPS. However, very limited data are available on the number of hospital days and drug trials required to select agents, the distribution of types of agents selected using the alternative methods, and arrhythmia recurrence, acute myocardial infarction, and mortality rates. Other studies have independently evaluated the efficacy of antiarrhythmic agents, again in a very limited fashion. Assessment of these alternative selection and evaluation methods requires data on all of these outcomes. The short term outcome of drug selection must be related to the long term outcomes of morbidity and mortality. The ESVEM trial mentioned earlier will provide some of this important information. Evaluation of the contribution that exercise testing can make to antiarrhythmic drug selection needs further attention. The consequences and potential benefits of sequential use of these diagnostic technologies must be empirically evaluated. Most studies have considered these methods in isolation when the maximum benefit (and possibly minimum long-term costs) may be achieved when these alternatives are used in an optimal sequence.

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TABLE III-1

Estimates of Patient Eligibility for Alternative Evaluation Procedures

Study	Evaluation Procedure (% of Patients Eligible)						
	Both	ACM	ACM only	ACM Exercise	EPS	EPS only	Neither
Swerdlow & Pederson 1982		50			82		10
Kim et al 1986	46	60					10
Mitchell et al. 1987	53.4	66.7	13.3	62	82	28.6	3.8
Bigger et al. 1986					80		
Lampert et al. 1988		73					
Base Case Estimates[1]		59		55[2]	81		

[1] Base Case Estimates are derived by taking the mean of all estimates available. A sensitivity analysis is performed substituting the lowest and highest estimates available.

[2] Mitchell et al. 1987 reported that 7% of patients were unable to undergo exercise testing in any form. Therefore, the Base Case Estimate for ACM was reduced by 7% to obtain an estimate for ACM/Exercise testing eligibility.

ACM = All patients who qualify for Ambulatory Cardiac Monitoring
ACM only = Patients who qualify for ACM but not EPS
EPS = All patients who qualify for Electrophysiologic Studies
EPS only = Patients who qualify for EPS but not ACM
ACM Exercise = All patients who qualify for ACM/Exercise Testing
Both = Patients who qualify for either ACM or EPS
Neither = Patients who qualify for neither ACM nor EPS

TABLE III-2

Criteria for Drug Efficacy

Study	Ambulatory Cardiac Monitoring				Electrophysiologic Studies
	VPDs(% Decrease)				
	Frequency	Paired	Repetitive	Runs	
Mitchell et al 1987	80	90	100		< 6 consec VPDs
Mason et al 1989	70	80	90	100	failure to induce run of VT >15 consec complexes
CAPS 1986	70			90	
CAST 1989	≥80			≥90	

Table III-3

Comparison of Outcomes: Ambulatory Cardiac Monitoring (ACM) versus Electrophysiologic Studies (EPS)*

Outcome	ACM (n= 29)	EPS (n= 28)
Effective Drug	100%	54%
Amiodarone	24%	46%
Change in Drug during Follow-up	38%	40%
VT Recurrence Rate	45%	18%
Sudden Death	7%	3.5%
Total Mortality	19%	19%
Hospital Days	20 ± 15	30 ± 26
Drug Trials	3.2 ± 1.8	5.5 ± 2.8

* These data are derived from Mitchell et al. 1987

Table III-4

Model I : Sensitivity Analysis

Probability	Base Case Value	Threshold Value
Qualify EPS	0.81	0.83
Qualify ACM/Ex	0.55	0.65
Select EPS	0.54	0.55
Select ACM/Ex	0.69	0.81
Utility		
Select-	0.00	0.50

Table III-5

Model II : Sensitivity Analysis

Probability	Base Case Value	Threshold Value
Qualify EPS	0.81	None
Qualify ACM/Ex	0.55	0.84
Select EPS	0.54	0.67
Select ACM/Ex	0.69	0.90

Figure 1 Decision Model I

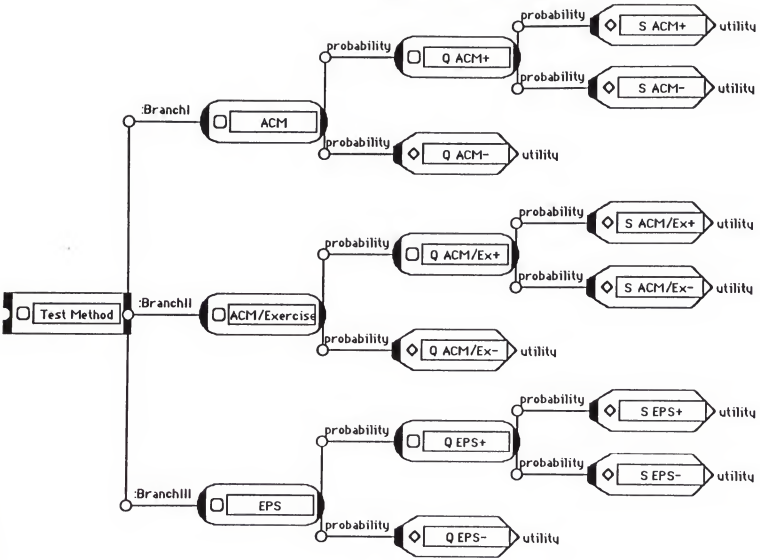


Figure 1a Selection Rate

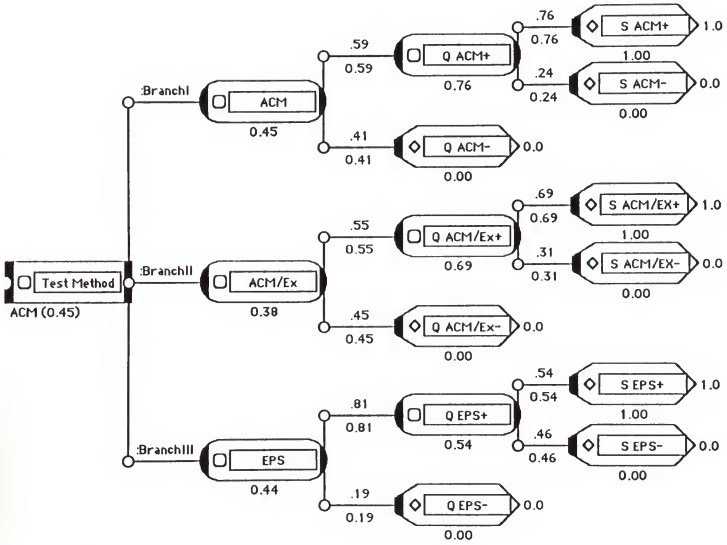


Figure 1b Recurrence Free

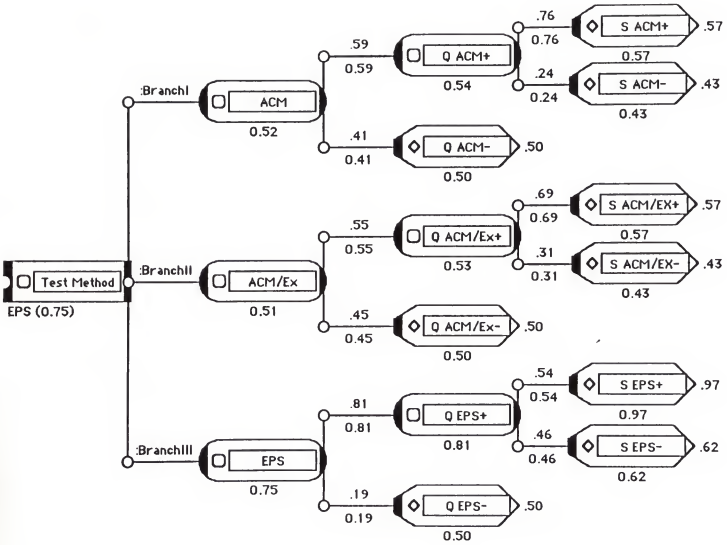


Figure 2 Decision Model II

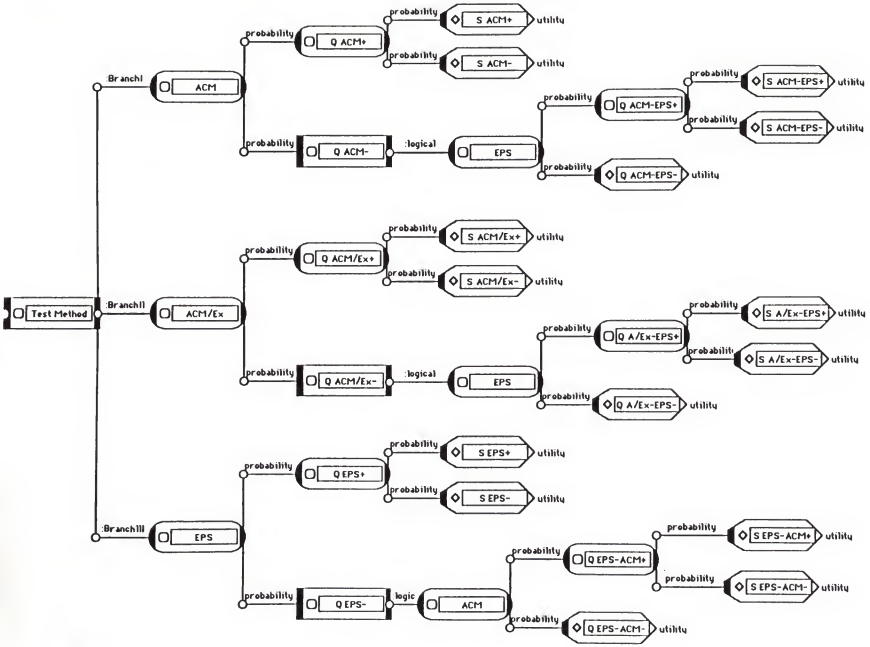


Figure 2a Estimates

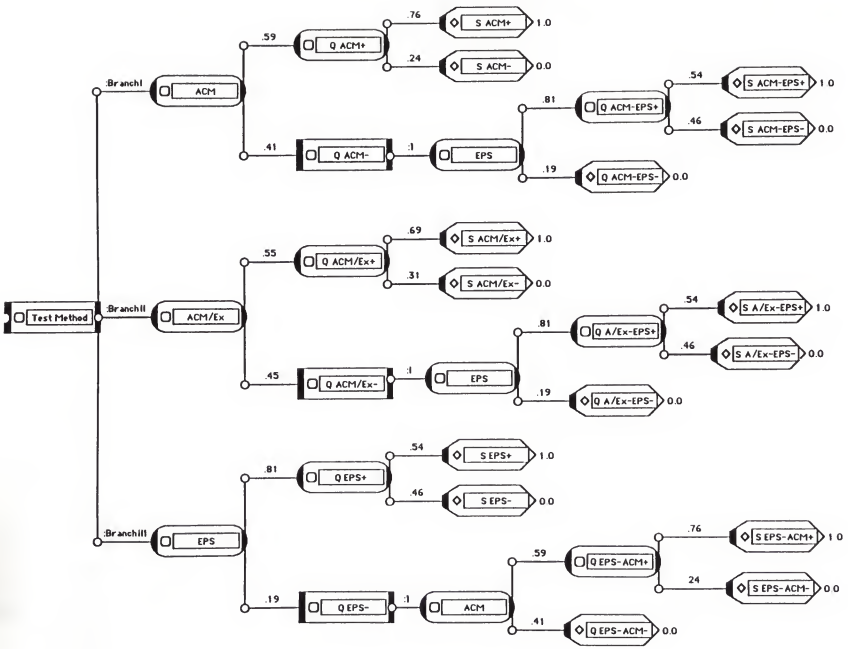


Figure 2b Selection Rate

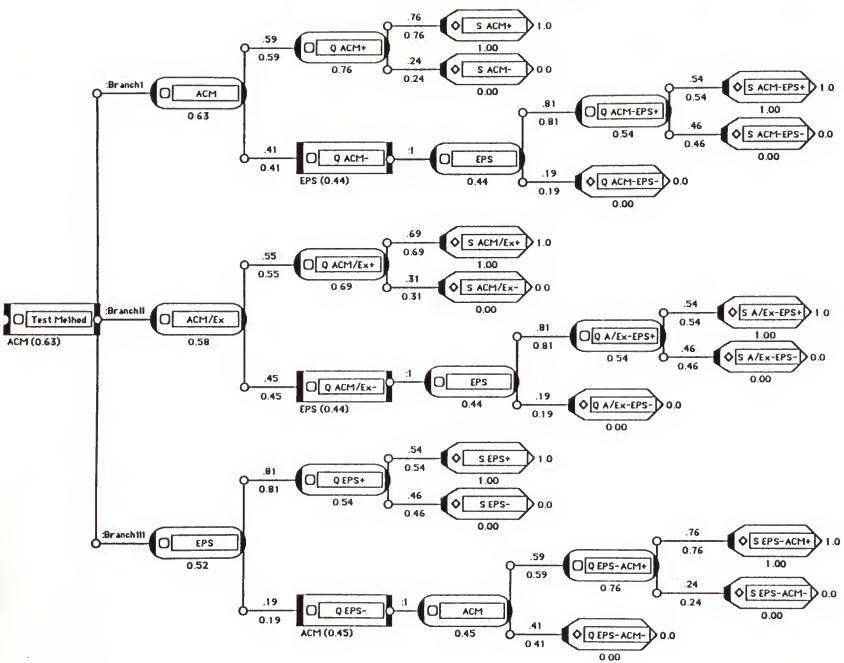


Figure 2c Recurrence Free

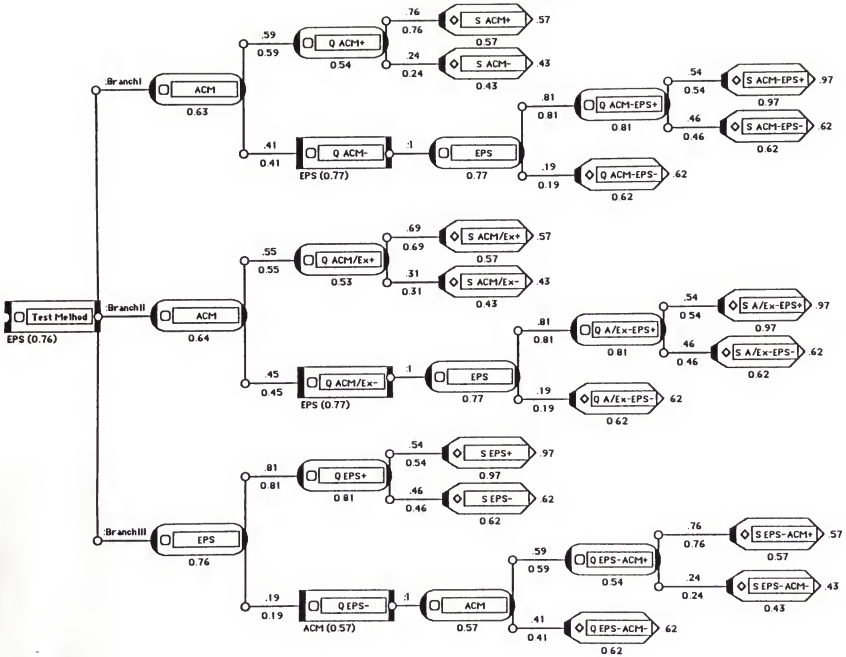


Figure 2d Hospital Days

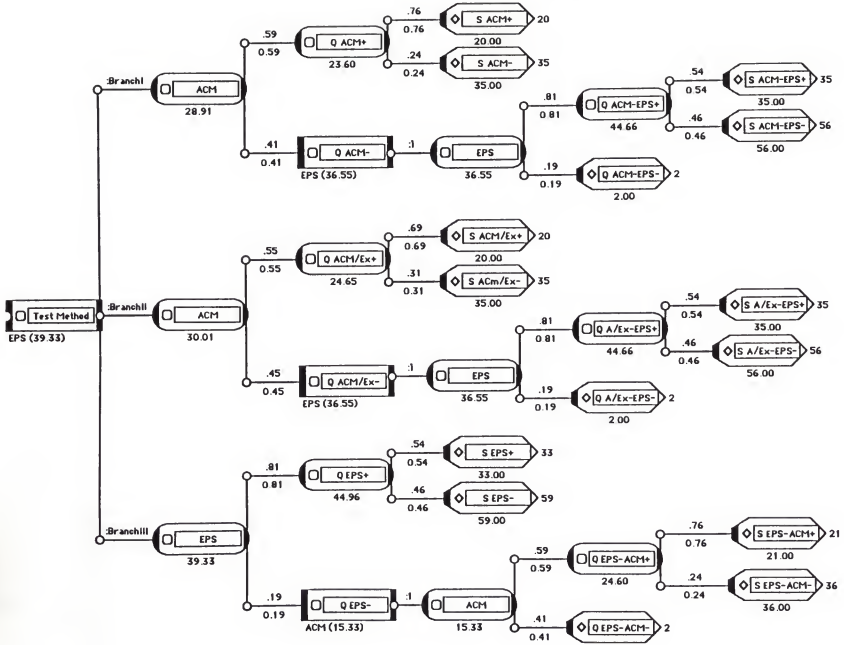
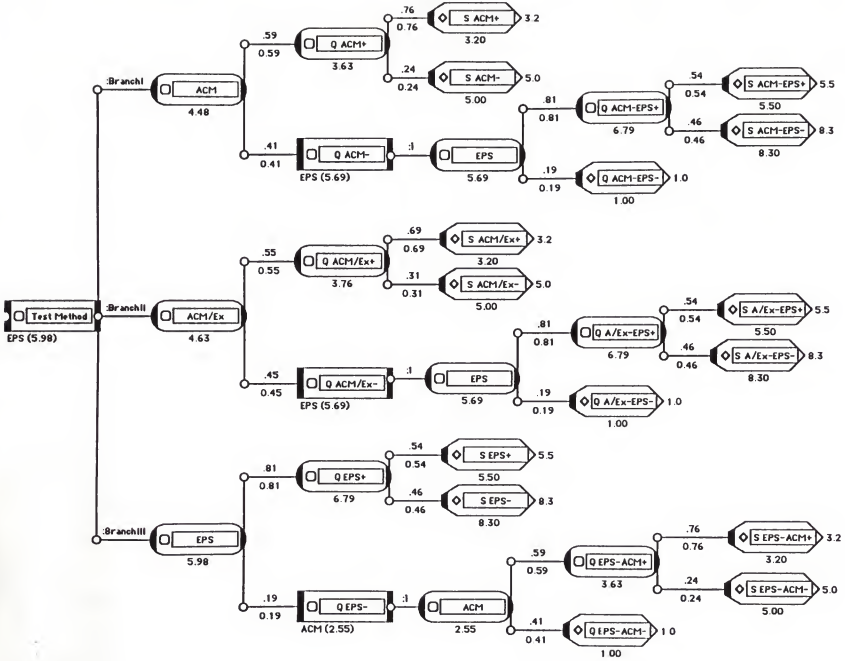


Figure 2e Drug Trials



Appendix IIIA

Abbreviations used in Decision Models.

ACM = Ambulatory Cardiac Monitoring

ACM/Ex= Ambulatory Cardiac Monitoring with Exercise Testing

EPS = Electrophysiologic Studies

Q = Probability of **qualifying** for the respective methods

S = Probability of having an antiarrhythmic agent **selected** by the respective methods

Examples:

Q ACM+ = probability of qualifying for ACM

S ACM- = probability of not being able to select an agent using ACM

Q ACM-EPS+ = probability of failing to qualify for ACM, then qualifying for EPS

S ACM-EPS- = probability of failing to qualify for ACM and then not being able to select an agent using EPS

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